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DRUG THERAPY IN DEGENERATIVE DISEASE

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The term degeneration is used physiologically to refer to a process characterized by an impairment or perversion of the function of a tissue. It should be noted that with this definition cancer would be classified as a degeneration, and the expression "carcinomatous degeneration" of a tissue is not infrequently used.

Morphologically the degenerations form a heterogeneous group of changes in which abnormal materials collect in or between cells, with nonfatal or fatal consequences. The degenerations are believed to be due either to the metabolic disorder of cells, which arise from latent weaknesses in the constitution, or from external causative factors or a combination of both. The morphologic changes consist of "cloudy swelling," or albuminous degeneration, fatty degeneration, glycogen infiltration, amyloid degeneration, hyaline degeneration which involves collagenous connective tissue in arteriosclerosis, mucoid degeneration and the excessive deposit of urates, pigments, calcium and other substances and of the necrosis of cells.

The expression "degenerative diseases," however, refers particularly to the slowly progressive circulatory and metabolic disorders usually associated with aging. In contrast to the infectious diseases of youth, the causation of degenerative diseases appears to be chiefly endogenous, cumulative and multiple, the onset insidious and asymptomatic and the course chronic, progressive and nonimmunizing.[1]

It is rational to distinguish between the "degenerative diseases" and the processes, retrogressive or degenerative, which occur as a natural concomitant of life. Or, in other words, it is rational to distinguish between pathologic aging and physiologic aging.[2] In pathologic aging the degenerations are accelerated by some external or internal environmental factor or factors which, if known, would be subject to control. On the other hand, in physiologic aging, or senescence, the degenerations are viewed as an involution or as a retrogressive process which is as natural as growth. This view would teach that, in the process of living, injurious chemical and physical conditions accumulate because of the imperfect adaptation of the body to its environment, and, as a result, the usual degenerative changes associated with aging occur, including the cancerous processes.

The degenerative diseases, then, are the noninfectious and nonparasitic diseases which kill and maim aging persons prematurely and for which it is biologically rational to hope that the causes, the prevention and better management may be found.

SOME OF THE DEGENERATIVE DISEASES

Some of the more important or better known degenerative diseases will be listed, for purposes of orientation, relative to treatment with drugs. Arteriosclerosis, chronic myocarditis, chronic nephritis, atrophic gastroenteritis, pernicious anemia, diabetes mellitus, cirrhosis of the liver and the pancreas, diverticulosis of the colon, hemorrhoids, senile paralysis agitans, senile psychosis, multiple sclerosis and combined degeneration of the spinal cord, hypertrophy of the prostate gland, dental caries (perhaps), hypertrophic osteoarthritis, postmenopausal or senile osteoporosis, gout, otosclerosis and senile deafness and blindness constitute some of the degenerative diseases. Some would classify cancer and goiter as degenerative diseases. The decline of function of the ovaries and the testes with age represents involution rather than degenerative disease.

DRUGS USED IN THE MANAGEMENT OF DEGENERATIVE DISEASE

The drugs which are used to substitute for specific deficiencies created by the degeneration of organs are relatively few in number and involve, with two exceptions, endocrine products. The specific drugs used to substitute for functions lost as a result of degenerative disease or the natural involution of an organ are: insulin for diabetes mellitus, extract of adrenal cortex for adrenal cortical insufficiency or Addison's disease, thyroid for myxedema and diseases fostered by hypometabolism, extract of liver for pernicious anemia which results from a type of atrophic gastroenteritis, pancreatin for the deficiency of pancreatic juice due to pancreatic fibrosis, estrogens for menopausal symptoms and associated disturbances and cancer of the prostate gland and testosterone to improve the retention of protein and for the treatment of cancer of the breast. All the other drugs used in the management of degenerative diseases act primarily by ameliorat-

Read at the Midyear Meeting of the American Pharmaceutical Manufacturers' Association (in connection with the Scientific Award to the American Medical Association), New York, Dec. 16, 1947.

1. Stieglitz, E. J.: Geriatric Medicine, Philadelphia, W. B. Saunders Company, 1943.
2. Rolleston, H.: Medical Aspects of Old Age, New York, The Macmillan Company, 1932.

ing the symptoms of disease rather than by substituting for a deficiency.

Vasodilators, such as theobromine, theophylline ethylenediamine, the nitrites, erythrityl tetranitrate, bismuth subnitrate, nicotinic acid, papaverine hydrochloride and alcohol, are used to counteract vasospasm or dilate relatively inelastic arterioles.

Sedatives, such as the barbiturates, chloral hydrate and the bromides, are used in hypertension and coronary disease to promote relaxation and decrease the load on the heart. Drugs which support the heart, such as digitalis, strophanthin and quinidine sulfate, are frequently required. Expectorants, such as potassium iodide and ammonium chloride, are useful in cardiac asthma and emphysema. Diuretics, the purine derivatives, the organic mercurials and ammonium chloride are of value in cardiac edema and some cases of cirrhosis of the liver.

Analgesics, such as morphine for the pain of coronary occlusion and the salicylates for rheumatic pains, prevent much suffering.

Antispasmodics, such as belladonna and stramonium, find a place in the management of paralysis agitans. Colchicine promotes the excretion of uric acid in gout and probably acts on the cause as well as the symptoms.

Antibiotics and sulfonamide drugs will probably retard the development of certain degenerative diseases by shortening the duration and decreasing the severity of infectious diseases.

Though there have been striking achievements in the treatment of degenerative disease, the outstanding achievement of medical science has been the control of infectious diseases. This achievement is dramatically demonstrated by mortality and longevity statistics. In 1900 the life expectancy was 49 years; in 1945 it was 66 years. Thirty per cent of persons who now have attained the age of 65 owe their survival to advances in medicine and public health administration made since they were born.[3] In addition to saving more and more lives, the application of medical discoveries, since 1900, has added four years to the life expectancy of those who are now 40 years of age, and one and a half years to the life expectancy of those who are now 65 years of age. (In 1945 the life expectancy of men at 65 was twelve and four-tenths years and of women fourteen and a quarter years.) Medical progress has not only saved more lives but it has added a few years to the average life. However, the added years are probably derived more from the control of infectious disease than from the control of degenerative disease.

While many have been reaping the harvest of the achievements of medical science, public health administration and pharmaceutic chemistry, a change has been occurring in the structure of the population and in the need for emphasis on a new area of medical research. As a result of a decrease in birth rate (12.1 in 1900 and 8.3 in 1940), a decrease in immigration and an increase in persons surviving into middle and old age, the population has been shifting from youth to middle age. Almost 29 per cent of the population in this country are over 45 years of age; by 1960, 33 per cent will be over 45 years of age; 7.7 per cent, or almost 11,000,000 persons, in this country are now over 65 years of age, and by 1960, 9 per cent of the population will be over 65 years of age. This shift in population will probably occur more rapidly than is now predictable, because the mortality from pneumonia, tuberculosis and other infectious diseases is rapidly decreasing. This means that the emphasis in medical research will have to be changed and the public health program will have to be broadened.

I believe that this is a turning point in the history of medical research. The emphasis in the past, and properly so, has been on the control of the acute diseases, which, except for the virus diseases, have largely been brought under control. In the future, the emphasis must be on the chronic and degenerative diseases. The importance and urgency of this situation may be illustrated by presenting some evidence. For example, chronic cardiac disease, cancerous arteriosclerosis, cerebral hemorrhage, chronic nephritis and diabetes mellitus now rank among the first ten causes of death and account for 60 per cent of deaths in the United States. More dramatically, one half of the babies born in 1940 will die of degenerative disease of the circulatory system and kidneys. Moreover, middle and old age are characterized by a high incidence of disabling disease. Seventy per cent of persons now permanently disabled are 45 years or more of age. Thirty per cent of the patients admitted to mental hospitals are 60 years of age or more, most of which patients have senile psychosis due to cerebral arteriosclerosis. Six million and eight hundred thousand persons have rheumatism, and of these 1,500,000 have the degenerative form of arthritis, namely, hypertrophic osteoarthritis. One hundred and fifty thousand persons are now invalided by their rheumatic condition.

It seems clear that unless medical research discovers a way to decrease the disabilities incident to chronic illness and incapacitation of middle and old age, economy and medical practice, as it is known today, will undergo much change. The total number of sick persons will obviously increase, because of the long periods of disability. This will increase the need for physicians and nurses and for beds for hospital and custodial care. The total cost of medical care will be increased beyond that anticipated by an increase in population alone. These rather obvious facts show that since the turn of the century medical advances have been creating an obligation for future generations to care for proportionately many more old and disabled persons than are now being cared for. The only way this obligation can be lightened is by the expenditure of more money and time on research on degenerative disease.

Therefore, it seems clear that "to prolong useful life" is the next important contribution to be made by medicine and pharmaceutic chemistry. One of the first needs is to dispel the fatalism which surrounds the subject of degenerative disease, a fatalism which is based on a failure to learn and recognize the implications of knowledge now available. Within the last twenty years unequivocal progress has been made in the treatment of cancer, and there are reasons to believe that arterial disease may be brought under control. For instance, let me illustrate by using arteriosclerosis as an example, since

3. Dublin, L. I.: Human Biol. **13**: 439, 1941; **14**: 352, 1942.

V 13
1948

it is the major degenerative disease responsible for the failure of the function of such vital organs as the heart, kidneys and brain. The following facts establish the view that something can be done about arteriosclerosis. *(a)* All persons over 80 years of age do not have decided arteriosclerosis when they die. Groddeck,[4] in autopsies of 283 persons over 80 years of age, observed that 34 per cent had only slight sclerosis of the coronaries and 3 per cent had only minimal sclerosis of the aorta. *(b)* Arteriosclerosis does not appear with equal frequency in the sexes, which is particularly true of coronary disease. *(c)* Coronary disease is more common in white persons than in Negroes.[5] *(d)* Arteriosclerosis is not uniformly distributed throughout the vascular system. *(e)* It occurs in association with renal disease and infections in children; hence it is not solely correlated with age. *(f)* It can be produced experimentally in animals by many different procedures, and its development may be modified by various drugs and procedures.[6] Numerous pathologists likewise express the belief that arteriosclerosis, such as effects the intima of arteries, is a disease and not the direct result of involution associated with aging.[7] The incidence of the disease is low in Iceland,[8] which is attributed to the high intake of iodine in food. Because of the relative complexity of the problem of the degenerative diseases and the time factor involved, the solution of this problem will be more difficult and expensive than the solution of problems presented by infectious and acute diseases.

SUMMARY

Progress has been made in the drug therapy of degenerative diseases, but it has been small in relation to the importance of the subject. The remarkable success which has attended the discovery of the cause, prevention and treatment of infectious and acute diseases has dramatically increased the need for the solution of the problem of the treatment of degenerative diseases. As a result of saving more lives in youth, the population has shifted from youth to middle and old age. This is a turning point in the history of medical research; the emphasis from now on will be on chronic illness and degenerative diseases. Unless something is done to prevent it, one half of the babies born in 1940 will die of degenerative disease of the circulatory system and kidneys. The achievements of the past two or three generations have rendered it necessary for future generations to care for many more old and disabled persons than are now being cared for. The next important contribution to be made by medicine and pharmaceutic chemistry is to prolong the period of useful life. There is plenty of evidence to show that cancer and degenerative diseases, such as arteriosclerosis, can be brought under control. However, the problem is more complex and its solution will require more man-hours and money than will that of the problem of infectious diseases. A society and profession which has promoted research to save human life has the responsibility of keeping that life in health.

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CHRONIC BRUCELLOSIS

Conclusions on Treatment After Ten Years

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Only within recent years has chronic brucellosis (undulant fever) been recognized[1] as an important cause of many common complaints of a chronic or recurrent nature. The most frequent symptoms[2] are fatigability, myalgia, arthralgia, neuralgia, headaches, light-headedness, intractable eye fatigue, sweating, thermolability, myriad digestive dysfunctions, nasal catarrh or chronic sore throat or cough, tachycardia, nervous irritability, depression, insomnia or mental torpor and various disturbances of the reproductive system, especially in the female. The commonest physical findings,[1p] when there are any, are low grade fever, slightly enlarged liver, increased redness of mucous membranes, tenderness in the right lower quadrant of the abdomen and a suggestive blood picture.[1i]

The typical history is one of long duration, varied diagnoses, unsuccessful treatment, recurrent course, aggravation of debility following pregnancy, operation or "influenza" and, finally, a conclusion that the patient must be "neurotic" or the complaints "functional" or constitutional. The well known acute phase of classic brucellosis is often not discoverable in the history at all.

It may seem incredible that such a disease could have been in the population for many generations and yet have escaped detection and recognition as a common clinical entity. The reason is probably at least fourfold: 1. The laboratory procedures which usually detect the acute form of brucellosis more often give negative results in cases of chronic brucellosis.[3] 2. The manifestations of chronic brucellosis are so varied that the disease is easily misdiagnosed as one of many other conditions which it may simulate rather well.[1j,k] 3. Organ diagnoses (cholecystitis, colitis, appendicitis, endometritis, sinusitis, arthritis) have too easily satisfied diagnosticians and surgeons. Brucella is capable of affecting any and every tissue of the body[1k]; and, while it is true that foci of uncontrolled brucellar infection or secondary infection often monopolize the clinical picture, the organism is rarely confined to any one organ. Often it is only after the necessary extirpation of the focus that it becomes clear that the patient is still sick with a generalized low grade infection. 4. Man and Brucella have probably been living together since the early herdsman stage of civilization. There has been a close adaptation between the two, so that the human organism reacts but little to this invader, and the latter seldom destroys its host. The task of detecting or excluding brucellosis has presented a serious challenge to diagnostic research. This problem has been considered in previous publications.[1n,p] The development of an adequate therapy for brucellosis is a difficulty of equal magnitude.

EXPERIENCE WITH TREATMENT

The purpose of this paper is to summarize my experience with treatment in 300 cases of chronic brucellosis, chiefly in California, since 1937. The

Owing to lack of space, the footnotes have been omitted from THE JOURNAL but will appear in the author's reprints.

diagnosis in these cases has been reported elsewhere.[1p] I began treating with a commercial heat-killed vaccine (Brucella abortus and Brucella suis) and "brucellin" (a preparation from pooled cultures of three species of Brucella),[4] in doses recommended in the folders which accompany the products. The objective seemed to be to give the patient a fairly severe local and general reaction, to jolt his resistive processes to a high point. Sometimes the results were gratifying and successful. More often the beneficial results were short lived or quite inconclusive. A common statement by the patient was: "I can't tell whether it is the vaccine that makes me feel worse or better, or whether it is just the natural ups and downs of my disease." In at least 25 per cent of patients the large doses of commercial vaccine caused severe exacerbations of symptoms without being followed by commensurate improvement. The muscles, skin and subcutaneous tissues of these patients became more and more intolerant of brucella vaccine. Large nodular indurations formed at the sites of injection and lasted many weeks. Some of these broke down into sterile abscesses a few months later. Others showed delayed healing of the needle wounds in the skin because of slight necrosis along the path of the needle tract. These hypersensitive patients became more sensitized with the large doses of commercial vaccine, and they could not, and would not, withstand such treatment. In spite of the high opsonin and agglutinin levels which developed, they felt worse, or no better, even after treatment was discontinued.

Summary of Early Experience.—In summary, then, I found that the usually recommended doses of commercial heat-killed brucella vaccine were not advisable as a general rule, for the following reasons:

1. *(a)* Only 60 per cent of patients with chronic brucellosis so treated were benefited at all by the treatment; *(b)* many of these relapsed later; *(c)* most of them objected to the discomfort and disability of this protein shock therapy.

2. Over 25 per cent of the patients with chronic brucellosis in California manifested hypersensitivity to brucella vaccine with this method. In practical terms, hypersensitivity means local tissue intolerance to vaccine, generalized exacerbation of symptoms and a short-lived increase in agglutinins and opsonins, which is deceptive.

From this study it appeared that agglutinins and opsonins may result from hypersensitivity or sensitization as well as from immunity. If the vaccine stimulated the production of immune bodies, the good effect was counteracted by the development of hypersensitivity at the same time. This offers an understanding of patients who are not well in spite of attaining laboratory evidence of immunologic response to infection. Although the blood may show agglutinins, opsonins and complement-fixing bodies, this immunity does not necessarily extend to the preferred habitat of the brucella, which is intracellular.[8] The invader, therefore, is often well protected from blood-borne antibodies and antibiotics.

Effect of Smaller Doses of Vaccine.—The next logical step was to decrease the size of doses of the vaccine in order to avoid excessive reactions. Two methods were used. The total quantity of material injected was kept very small, 0.01 to 0.40 cc., and the vaccine was diluted with sterile isotonic solution of sodium chloride to make weaker concentrations. Each local reaction was carefully noted as to size, redness, tenderness, hardness and duration. The intervals between injections were adjusted experimentally. After an interval of five days there often appeared an increased sensitivity to subsequent injections. It was found that the concentration of the vaccine was more important than the mass volume of the injection.

The results of diluting the vaccine to a few hundred or a few thousand killed bacteria per dose were distinctly better than the results of shock dose therapy. Patients felt less abused during treatment and were less inclined to give up vaccine therapy. A larger number (75 to 80 per cent) were significantly improved. Undulations of the disease were less frequent and severe. A larger number of patients received dramatic relief from discomfort and disability. Sterile abscesses and cutaneous necrosis became unusual, or even rare. Opsonins and agglutinins appeared more gradually. However, there were still 20 per cent of patients who could not tolerate these injections of killed bacteria in any dose and a large percentage in whom the doses could not be increased without increasing sensitivity. There were also a number of patients who still felt sick in spite of good local tissue tolerance to the vaccine and good opsonic response. Theoretically, they should have been getting better, but they had reached a plateau after their initial improvement. They remained better, not very sick, but making no progress, and certainly far from cured.

Following a suggestion of Harris,[1k] I attempted desensitization with intravenous injections of vaccine in doses of a few killed bacteria, the amount being increased gradually to several thousand per dose. With only 1 or 2 patients was this successful. The hypersensitive patients continued to become still more sensitized. The doses had to be decreased instead of increased in order to avoid successively severer general reactions and persisting exacerbations. I was unable to confirm Harris' impression that after a few intravenous injections the subcutaneous route could be resumed. However, the intravenous route became valuable in a small, important group of cases after I learned what doses to use.

Effect of Nonspecific Measures.—A number of physicians have discontinued brucella vaccine therapy entirely and have fallen back on general tonic measures. From my early experience, outlined in the preceding section, it is easy to see how one could become discouraged by the bizarre results of specific vaccine therapy of chronic brucellosis. Penicillin is useless in treatment of this disease.[1r] Sulfonamide compounds have also been disappointing[6] with few significant exceptions.[7] Streptomycin does not offer much hope when given in ordinary doses.[8] Streptomycin and sulfonamide compounds,[7e] like many other agents, may appear to cause remission in the acute form of undulant fever in which sudden remission usually occurs spontaneously. In cases of the chronic form of the disease the failure of these blood-borne drugs is probably due to the intracellular existence of brucellas in the tissues.[8]

V 13
1948

In order to test the effect of general tonic measures, I reviewed the literature and tried a number of recommended measures, without vaccine therapy. Crude liver extract; cacodylates (dimethyl arsenate); strychnine; vitamins; thyroid and other endocrine substances, as possibly indicated; salicylates, given intravenously; nitromersol N.F. ("metaphen"); congo red; iodides; colchicine, and numerous symptomatic remedies were used. As a group, patients with brucellosis did not do well on general tonic measures. Such patients feel that they need rest, but no amount of rest proves sufficient to overcome the disease in adults. The same is true of physical therapy. Almost every patient in my series had tried large doses of preparations of the vitamin B complex before coming to me. I concluded that general tonic measures are usually a discouraging waste of time, money and effort except for short periods of preparation for vaccine therapy. While waiting for the healing of necrotic lesions resulting from cutaneous tests or for the absorption of nodular reactions to vaccine, I give crude liver extract and adrenal cortex extract intramuscularly alternating with intravenous administration of vitamin B complex and a strychnine-cacodylate preparation. Only 2 patients of the 300 have improved so much on this regimen that they do not appear to need vaccine. However, both these patients have relapses when treatment is stopped for a long period.

Extreme Degrees of Hypersensitivity.—My next effort was to answer the question: How much must brucella vaccine be diluted before it can be tolerated by the most hypersensitive patients? Controlled experiments proved repeatedly that even 1 bacterium was too much for most of them! The vaccine is a solution of the specific substances, presumably proteins, of the brucella bacterium, an encapsulated coccoid bacillus, 2 to 3 microns long and about 2 microns wide. By further diluting the vaccine with saline solution and injecting it into patients, along with plain saline solution controls, I found that the sensitized human organism reacts to infinitesimal fractions of the specific substances of this microscopic pathogen. The soreness of the muscle, the redness of the skin and the induration of the tissues at the site of injection of the vaccine offer both objective and subjective proof that the dilution of the vaccine contains something not present in the diluent saline solution alone. When given intravenously, these dilutions of vaccine will produce in sensitized patients a mild to pronounced exacerbation of generalized aching, chills and fever, appearing in four to six hours and subsiding in another four to forty-eight hours.

To date, my colleagues and I have been unable to find a concentration of brucella vaccine so dilute that it fails to produce an objective reaction in the most sensitive patients with chronic brucellosis. Attempts to find such dilutions have taken us beyond the point where large protein molecules could be expected to be present, e.g., doses smaller than 1 bacterium $\times 10^{-14}$. Some specific brucella substances are polysaccharides, much smaller molecules than proteins.[9] These might explain the activity of the slightly weaker dilutions. Practically, it seems almost impossible to dilute these specific substances out of existence. Adsorption and fragmentation of specific molecules have been suggested in partial explanation of this apparent conflict with theory. By drastic cleaning technics, all known errors of adsorption have been eliminated. We have been encouraged to persist in these observations because of the similarity of brucellosis to tuberculosis and the well known allergenic properties of tuberculin in extreme dilution. Theoretic implications of these observations are being subjected to further study.

The significant clinical observation is that certain patients with extreme brucellar allergy are most difficult to desensitize unless doses of molecular size are used to initiate treatment.

Advantages of Oxidized Brucella Vaccine.—The work of Calder[1h] and Hagebusch and Frei[11] led to the use of a vaccine which is modified or attenuated by oxidation with nitrous acid in order to avoid severe reactions. The oxidized brucella vaccine was developed by Foshay, of the University of Cincinnati School of Medicine. It is prepared in a manner similar to his modification[10] of tularemia vaccine, which is well tolerated and provides protection to bacteriologists working with Pasteurella tularensis. Oxidized Br. abortus vaccine has never caused a sterile abscess or cutaneous necrosis. I agree with Calder that this vaccine is superior to any other known preparation for treatment of chronic brucellosis. However, it still causes severe local and general reactions in hypersensitive patients when used in doses of appreciable numbers of killed bacteria. Sensitivity likewise increases if the doses are increased too rapidly. During the war, supplies of oxidized vaccine were short. Commercial vaccine was often substituted, in identical doses, and it was obviously less well tolerated, apparently because it was more allergenic than Foshay's oxidized vaccine.

PRESENT THERAPY

Principles.—By avoiding general reactions entirely and striving to find the minimum dose which will produce a local reaction of not more than twenty-four hours' duration, a method of treatment has been evolved which enables me to treat individually every patient with chronic brucellosis with greater satisfaction than by any other therapy in my experience. The principles of the present method are as follows:

1. One should never begin vaccine therapy until all tissue reaction to previously administered vaccine or cutaneous tests has completely subsided. Initial intradermal tests should be made with very dilute materials, such as "brucellergen" (a suspensoid of nucleo proteins of brucella cells) diluted to 1:120,000 or doses of vaccine representing no more than 1,000,000 killed bacteria[11] in 0.05 cc. Sensitivity is always increased by necrotic reactions and by indurations due to unabsorbed vaccine. Desensitization is practically impossible as long as there is a breakdown of tissues anywhere in the body as a result of living brucellas or specific brucellar derivatives (allergens).

2. Treatment should begin with vaccine diluted (and preferably modified) so that the initial doses will probably be too small to produce any general reaction and will cause only a minimal local reaction, if any. For hypersensitive patients this may mean a dose of much less than 1 killed bacterium, preferably about 1 molecule of specific antigen.

3. Injections should be made into the muscles of the thigh and deltoid region in order to avoid the variable slower rates of absorption by the subcutaneous route.

4. Another injection of vaccine should never be given while there is any induration, redness, swelling or tenderness from the previous dose. The sites should be inspected and palpated; one should not accept the patient's word that the previous reaction has subsided.

5. Injections should be given every two or three days, as reactions permit. The intervals between doses should not be more than five days by whatever route the injection is given.

6. When there is only a minimal local reaction, subsequent doses may be doubled each time until larger reactions begin to appear. Then the doses should be increased by only 0.02 to 0.10 cc. The maximum dose reached in any one concentration or dilution of vaccine is 0.45 cc. After this dose is given, the next dose is 0.05 or 0.10 cc. of a dilution ten times as concentrated.

7. If reactions become progressively severer in spite of little or no increase in doses of vaccine, the injections should be stopped for five days or more and the series begun again with a much weaker dilution of vaccine than has ever before been used for the patient. The doses are increased more gradually. A different route, such as the intradermal [12] or the intravenous one,[1k] will be necessary for some patients.

8. Vaccine therapy may be discontinued when the patient is apparently recovered symptomatically and has a high phagocytic index which has been attained gradually without sensitization. In the case of young, vigorous patients this will require several weeks. For the majority of all patients it requires more than one year. The size of the final dose attained may be only a few killed bacteria when only desensitization is required, or it may be several billion killed bacteria in an undenatured vaccine when sensitivity is low.

9. If a patient is not recovered clinically after the gradual building up to large doses and a high phagocytic index, the following measures are indicated, in the order designated:

(a) Desensitize again, even though the patient's tissues do not appear to be hypersensitive.

(b) Search again for foci of infection, usually mixed, and give appropriate treatment with surgical measures or short wave diathermy, roentgen irradiation and medication, along with the vaccine. Investigate again the diagnosis as a whole.

(c) Repeat the desensitizing-immunizing series of injections with a vaccine of different strains of brucella, preferably from the geographic area where the patient contracted the disease.

(d) Try larger doses and greater concentrations of vaccine.

(e) Discontinue vaccine for an observation period of several months.

(f) Repeat the series, using a different route, either intradermal or intravenous, and increase the doses more gradually.

Additional Points of Treatment.—Dilutions of vaccine must be made with extreme accuracy and care to prevent contamination. We use 0.2 per cent phenol in the diluent. Dilutions should be kept fresh and cold and should be cultured periodically. The concentration of vaccine in the dilutions is seriously disturbed if a needle which has entered a strong dilution is used to prepare or administer weaker dilutions. Syringes are thoroughly cleansed after each use with detergents, soaked overnight in a concentrated solution of sulfuric acid and potassium bichromate and thoroughly rinsed before sterilizing. Needles are cleaned with detergents and soaked in 1 per cent sodium hydroxide-alcohol solution for one-half hour after each use, then rinsed well and sterilized. Sterilization is done by autoclaving or with dry heat, not by boiling in a common water bath. The supply of sterile isotonic solution of sodium chloride used for making dilutions and for cutaneous test controls must be rigorously protected from contamination with any needle, syringe, bottle or rubber stopper which might have even the minutest amount of brucella vaccine adhering to it. Failure to observe these precautions will result in inaccurate doses and erroneous conclusions.

Patients should be warned that they will continue to experience some of the natural undulations of their disease even while they are under treatment. They should be ordered to resume normal activity to the limit of their will power, short of exhaustion. Sedatives and nearly all other medications are to be discontinued within a few days or weeks after vaccine therapy is started. Most patients on special diets for "ulcer" and "colitis" can usually resume normal, adequate eating habits. A very few patients, until they are desensitized, may need to avoid milk and milk products, beef and pork which contain brucella substances to which they are allergic. Vacations from vaccine should be firmly discouraged because of the possible increase in sensitivity after five days. Intelligent patients can be taught in a few weeks to administer the vaccine to themselves, checking with the physician once or twice a month. Gratifying improvement is usually noticed within two months of beginning treatment.

V 13
1948

SUMMARY AND CONCLUSIONS

The difficulties in treating chronic brucellosis are examined.

Ten years' experience in the treatment of 300 patients by various schemes of specific vaccine therapy is reviewed. The usual methods of using brucella vaccine have been rather disappointing. Nevertheless, vaccine administered by an improved method appears to offer better results than any other management.

The chief obstacle to vaccine therapy was found to be the patient's sensitization to brucella substances. This hypersensitivity reached an extreme degree in about 25 per cent of cases in California.

A safe and effective method of treating chronic brucellosis with oxidized brucella vaccine has been developed and is reported in this paper. The principles involve desensitization with ultraminute fractions of oxidized brucellas before or after using larger doses.

Advantages of this therapy are that *(a)* it is applicable to nearly all cases of chronic brucellosis; *(b)* it is usually accompanied with symptomatic improvement instead of unpleasant reactions; *(c)* it is economical financially; and *(d)* it produces improvement, remissions or recoveries in 85 to 90 per cent of all cases.[13]

Disadvantages are that *(a)* a long time is required to complete the treatment in most cases; *(b)* old

persons and those with foci of infection and severe hypersensitivity are often difficult to treat, requiring much time, patience and interest on the part of both patient and physician, and *(c)* the vaccine should be specially prepared and requires meticulous care in diluting and handling. Permanence of remission or cure cannot be promised to patients because our experience with chronic brucellosis has been of too few years' duration.

Brucellosis is not a self-limited disease. In the chronic stage, it shows little or no tendency to spontaneous recovery in adult life. Treatment, even at best, is difficult and uncertain in effect. However, specific vaccine therapy, modified as reported here, offers a significant advance in the treatment and prognosis of chronic brucellosis.

RECENT PROGRESS IN NUTRITION AND ITS RELATION TO DRUG THERAPY

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The "Corpus" of Hippocrates not only lists many drugs, mainly of vegetable origin, but gives considerable space to a discussion of the regulation of the diet. However during the evolution of medical treatment much greater emphasis has been placed on drugs than on nutrition. This is not surprising, since as man sought food to satisfy his hunger he encountered a variety of substances which had a more or less immediate effect on the normal functions of the body. Many of these were prepared or concentrated so that they could be used to alleviate suffering or to combat disease.

The recognition of specific nutrients in the prevention of disease was impossible until a little over a hundred years ago because until that time all foods were assumed to supply a single universal nutrient. It is only within recent years that all the nutrients necessary for optimum nutrition have begun to be recognized and identified. Furthermore, druglike materials usually have an immediate effect, while the omission of an essential nutrient from the diet produces a deficiency only after a considerable lapse of time. Thus certain substances have been used variously as a therapeutic agent and as a source of an essential nutrient. One of the best examples is cod liver oil. Cod liver oil was recommended by the English physician Howel for the treatment of wounds as early as the fifteenth century. By 1730, Norwegian fishermen associated its use with the prevention of rickets. However, there was no explanation for its effect in either instance, and the scientific world hesitated to acknowledge its use. In 1837 cod liver oil was found to be a rich source of iodine, and on this basis it was entered in the pharmacopeia. However when other sources of iodine were found to be equally as effective its use fell into disrepute and cod liver oil was considered to have no greater value than other fats. In spite of this, people continued to use it and the pharmacists continued to keep it in stock. Sound basis for its use came only after careful animal experimentation had shown that cod liver oil would prevent both vitamin A and vitamin D deficiencies. Today cod liver oil is accurately standardized on the basis of its vitamin A and vitamin D content. In other words, if a vitamin or nutrient is to exhibit a pharmacologic action it must be used under specific pathologic conditions.

In spite of the greater emphasis on drugs, there has always been a close association between nutrition and drug therapy. Legislative control was combined in the Federal Food and Drug Act of 1906 and in the Federal Food, Drug and Cosmetic Act of 1938. The Council on Pharmacy and Chemistry of the American Medical Association, established in 1905, gave such considerable attention to foods that a Committee on Foods was established in 1929, which later became the Council on Foods and Nutrition. Increased knowledge of physiology has done much to give an insight into the mechanisms of the action of drugs on tissues and organs. Studies in nutrition have led to a greater degree of specificity in the use of drugs and have given a basis for the development of new specific therapeutic agents.

These relationships have been numerous, but I shall limit my discussion to those in three areas, namely, antianemic substances, amino acids and metabolic antagonists.

ANTIANEMIC SUBSTANCES

Iron therapy in anemia probably dates back to 1746, when Menghinis demonstrated the presence of iron in blood and claimed that the iron content could be increased by a diet rich in this element. However it was not until about 1830 that evidence was presented to show that the blood of chlorotic patients was low in iron and that the administration of iron increased the number of red blood cells. These observations gave rise to a large number of iron preparations for the treatment of anemia. These included insoluble forms, colloidal forms and ferric and ferrous forms. Many of these were widely used, but there was no agreement as to the efficacy of iron preparations in the treatment of simple anemia until 1928, when it was clearly established from animal studies that inorganic iron in the presence of copper is readily utilized for the synthesis of hemoglobin. Furthermore, it was shown that simple iron salts which are easily ionized are more readily utilized by the body than complex forms such as hemoglobin. It was also possible to obtain a rather definite answer concerning the relative value of ferric and ferrous forms of this element. This work clarified the knowledge regarding simple hypochromic anemia, allowed the preparation of standard forms of iron and also demonstrated that anemias which do not respond to an adequate supply of iron and copper must be due to the lack of other nutrients. Anemia due to iron deficiency was recognized as a secondary or nutritional anemia, but the so-called pernicious anemia was considered to be far removed from the state of nutrition. Pernicious or primary anemia, first described by Addison in 1849, differed from secondary anemia in the absence of a recognized cause and in the failure to respond to forms of treatment effective in other forms of the disease. In 1926-1927 Minot and Murphy reported that a number of patients suffering from pernicious anemia responded to the daily administration of 250 to 500 Gm. of mammalian liver. This immediately placed liver in the field of drug therapy, and I suppose that the reason liver had not been used previously was because it was

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needed in such large quantities. Anti-pernicious-anemia concentrates were prepared in large volume by many pharmaceutical companies. Great difficulty was encountered in standardizing the products because in the absence of animal assays it was necessary to test all the preparations on human subjects. Even so, excellent concentrates were manufactured, and these preparations were standardized and accepted in the "United States Pharmacopeia."

It is not surprising that pernicious anemia was not produced in experimental animals when only a few of the vitamins were recognized. In order to keep the animals alive long enough for changes in the blood to occur it was necessary to add several crude concentrates, and these could easily carry unknown factors. However, as each new member of the vitamin B complex became available in pure form, workers had a new hope that a pernicious-anemia-like condition might be produced. Each new attempt ended in failure, and finally it was found that rats could be maintained for long periods with no evidence of anemia on highly purified rations in which all the B vitamins were supplied in synthetic form. If a pernicious anemia factor or an extrinsic factor were required by this animal, where was the required supply obtained? It was only through the use of the newly discovered sulfonamide drugs that additional deficiencies were produced in the rat. When sulfaguanidine was added to the basal ration of a young rat, growth retardation resulted, and later it was found that there was a constant development of leukopenia and agranulocytosis. The condition was prevented with whole liver and with many liver extracts known to be rich in the anti-pernicious-anemia factor. But the anemia was not severe, and it was not a characteristic macrocytic anemia. Today it is known that the addition of the sulfonamide drugs decreased the synthesis of folic acid and biotin by the bacteria in the intestinal tract and that the blood dyscrasias developed largely because of a folic acid deficiency. In this connection it is interesting to note that the incidence of agranulocytopenia increased from 3 per cent among patients admitted to a children's hospital before the introduction of sulfonamide medication to a maximum of 12 per cent in 1942, when the use of sulfadiazine was at its peak. Folic acid therapy has been found to be of considerable value in the treatment of these patients. Studies in the field of nutrition, therefore, developed a means of combating the secondary effect of some of the sulfonamide drugs.

The greatest progress in the development of the knowledge of folic acid came from the use of microorganisms and chicks. As early as 1939 Hogan and Parrott found that chicks placed on purified rations which were adequate for the rat grew normally when 4 per cent of a water extract of liver was used but that anemia developed when it was used at lower levels. Similar studies were in progress in the laboratory at the University of Wisconsin when Snell and Peterson were working on a factor necessary for the growth of the Lactobacillus casei, and when preparations containing the bacteria were fed to chickens receiving purified rations containing all the known vitamins, normal growth and hemoglobin formation were obtained. The use of microbiologic assays facilitated the final isolation, characterization and synthesis of folic acid, or pteroylglutamic acid, by the workers at the Parke-Davis and Lederle laboratories.

The availability of synthetic folic acid has permitted its use in addisonian anemia, in nutritional macrocytic anemia and in sprue. It is now generally recognized that its action is not complete, but I am not competent to discuss the details of the relationship in human therapy. However, I do want to emphasize that with the availability of this substance it has been possible to extend studies on animal nutrition so that further knowledge may be gained regarding other anti-anemic substances. For example, chicks fed a synthetic diet will develop normally if folic acid is supplied in addition to the other known B vitamins. However, if certain natural rations containing soy bean oil meal and corn meal are used, a retardation in growth results, which is prevented by the administration of highly purified anti-pernicious-anemia preparations. These preparations contain extremely small amounts of folic acid. Somewhat similar results are obtained in the rats, but the results are much more erratic, undoubtedly because of a greater degree of intestinal synthesis. It is important to point out that neither of these species of animals shows anemia and that the only apparent deficiency is lack of growth.

Dogs develop remarkably well on synthetic diets containing no folic acid, but by the elimination of one of the known vitamins, especially nicotinic acid, a conditioned deficiency can be produced which will also respond to highly purified pernicious anemia preparations. In this instance an anemia does develop which may be called a macrocytic anemia. I do not wish to conclude that the substance active in the dog is the classic anti-pernicious-anemia factor, but it is important to point out that these new methods give a means of measuring additional factors and that eventually the production of true pernicious-anemia-like conditions in an animal should be possible.

Furthermore, deficiencies can be produced in animals such as the monkey, the mink and the fox which do not respond to pernicious anemia preparations but do respond to the addition of whole liver or raw milk. The activity in the whole liver can be concentrated, and it now appears that there may be more than one additional factor. It is also interesting that in both the monkey and the mink certain paralytic symptoms appear which may possibly be related to the degenerative conditions seen in human pernicious anemia and which may be aggravated when pure folic acid is used rather than liver preparations. It is interesting to recall that most of the experimental work on iron and copper has been done with milk diets, and now milk has been shown to contain the additional factors needed for hemopoiesis.

At the present time folic acid has not replaced liver preparations and it cannot be said that there are clearcut methods for the assay of pernicious anemia activity, but it is evident that there is a closer approximation to a complete understanding of the syndrome.

Furthermore, pernicious anemia is undoubtedly a disease of nutritional origin, although the relationship is complicated by the indirect effect of the production and destruction of nutrients in the intestinal tract by the bacteria. So-called synthetic

V 13
1948

diets may yield a more favorable environment for organisms producing needed vitamins than the mixtures of natural foods which man relies on. Conditioned deficiencies may therefore develop which can be overcome by the addition of factors which normally do not need to be supplied preformed in the diet.

AMINO ACIDS

Proteins have been given little consideration as therapeutic agents, undoubtedly for two reasons. First, proteins must be supplied in large amounts in order to produce a significant effect, and, secondly, medical workers have for many years felt that the protein content of the diet should be decreased rather than increased. During the past few years there has been a tremendous change in this point of view, and at the present time there is much interest in increasing the intake of protein in many pathologic conditions and also a greater interest in the use of protein hydrolysates and amino acid mixtures than in the use of intact proteins. Much of this interest is undoubtedly due to the fact that nutrition workers have clearly demonstrated that a deficiency of amino acids may develop much more rapidly than a deficiency of vitamins or minerals. Knowledge in this field has accumulated because it is now possible to feed animals a diet complete in all factors except protein or amino acids and because of the improved methods for the estimation of individual amino acids. One of the problems encountered in the use of free amino acids is that of imbalance. The importance of imbalance grew out of the early work in which it was shown that the addition of 40 parts of corn to a synthetic diet containing 15 per cent protein and no nicotinic acid produced a marked retardation in the rate of growth of rats. This retardation was completely counteracted by the addition of a small amount of nicotinic acid, and later it was shown that tryptophane had the same effect. Further work has shown that other proteins low in tryptophane, such as gelatin, produce the same effect as that observed with the corn rations. In fact, if 2 per cent of an acid-hydrolyzed casein is added to a ration containing 9 per cent of casein, a notable retardation in growth occurs. This reduced growth is corrected with the use of either nicotinic acid or tryptophane. If 2 per cent of unhydrolyzed casein is used, an increased rate of growth results. The toxic effect of the acid-hydrolyzed casein is not due to any injurious substance formed during the hydrolysis since a mixture of pure amino acids compounded to be equal to 2 per cent of the acid-hydrolyzed casein produces the same effect. Apparently in the absence of tryptophane certain amino acids have a definite injurious effect when fed at increased levels and in the free form.

Further work has shown that the amino acids most active in this respect are threonine and phenylalanine. It has also been shown that the injection of threonine has the same effect as the oral administration. It is clear, therefore, that in spite of the potential possibilities in the use of amino acid combinations there is much to learn regarding the proper concentrations of the individual amino acids in these mixtures.

Can a mixture of pure amino acids completely replace proteins in a diet? The answer to this question apparently depends largely on the age of the animal used. For example, Cannon and his coworkers have used mature rats and have subjected them to a protein depletion. When these depleted animals were given a mixture of sixteen amino acids patterned after the composition of casein, the gain in weight was identical to that obtained when they were given a comparable amount of casein. In other words no evidence for the need of an accessory factor to promote the utilization of these amino acids was obtained. Woolley, working with young mice, has found that when they are given a purified ration in which the nitrogen source is a supplemented casein hydrolysate maximum growth is not obtained until certain proteins or concentrates from these proteins are added. He has shown that the activity of different proteins is similar to their strepogenin content as determined with L. casei. My colleagues and I have worked in our laboratory with weanling rats and have obtained a growth of as much as 3 Gm. per day by using a mixture of the ten essential amino acids supplemented with glutamic acid to provide a total nitrogen content equal to that supplied by 10 per cent of casein. The addition of small amounts of intact proteins at the expense of glutamic acid gave only a slight increase in the rate of growth. It appears, therefore, that if intact casein contains a growth-promoting factor for rats other than the essential amino acids then the concentration in casein is too low to satisfy the requirement. Rose has reported the existence of a growth factor for rats in casein which has properties in common with strepogenin. In the light of the work on amino acid imbalance it is apparent that each amino acid must be supplied in optimum concentration before the need for accessory peptide-containing compounds can definitely be settled. In fact the excretion of many of the amino acids in the urine is increased when proteins of poor quality are fed, which means that the amino acid pattern is not optimal for use as fed to rats and mice.

This leads to the interesting observation that has recently been made regarding the rate of liberation of different amino acids from a given protein. For example, in casein the essential amino acids seem to be liberated at a more rapid rate than the nonessential ones. Cystine seems to be liberated at an extremely slow rate. Heat treatment of different proteins also alters the rates at which the amino acids are liberated. Perhaps there is a definite pattern of liberation which will give optimum utilization of the essential amino acids and which also influences the intestinal flora in such a way as to give better nutrition. In any case the kind and the amount of amino acids as well as the rate at which they are supplied to human beings may have an important bearing not only on adequate protein intake but on total nutrition. The availability of protein hydrolysates and free amino acids will do much to facilitate studies necessary to clarify this relationship and will be useful in supplementing diets shown to be inadequate on this basis.

METABOLIC ANTAGONISTS

As I indicated earlier, the introduction of drug-like materials in therapy has been dependent largely on trial and error. It is only recently that chemical constitution has been closely correlated with biologic activity. The developments in nutrition have done much to make studies possible.

In the first place, metabolic studies can be carried out only when it is possible to feed an adequate and known diet. Secondly, the availability of many of the nutrients in pure and synthetic form has allowed modification in the structure of these compounds. Out of this work has come the general recognition that slight modifications in the structure of certain vitamins may change them from essential nutrients to metabolic antagonists. A relationship of this kind was encountered in 1937, when the anti-blacktongue activity of a number of derivatives of nicotinic acid was studied. In this work it was found that 3-acetylpyridine actually aggravated the blacktongue condition in dogs. The significance of this observation was not realized until Woolley extended his studies on the biochemical antagonism. The work which attracted greatest attention was that of Woods and Fildes, who showed that para-aminobenzoic acid has antisulfonamide activity. This effect was explained on the basis that para-aminobenzoic acid is an essential nutrient and that the sulfonamide compounds functioned by interfering competitively with para-aminobenzoic acid. The discovery of this relationship prompted attempts to produce similar structural changes in other vitamins in the hope of producing other bacteriostatic compounds. The growth of certain bacteria was inhibited by 3-pyridinesulfonic acid, and the inhibition was reversed with nicotinic acid. "Pantoyltaurine" likewise produced bacteriostasis, which was reversed by pantothenic acid. Although much of the early work was done with bacteria, it was soon recognized that severe vitamin deficiencies could be produced through the use of antivitamins related to thiamine, riboflavin, vitamin K, vitamin E, biotin and other factors. Of great interest is the recent work on the use of 7-methyl folic acid in the production of a more severe anemia in experimental animals. This effect appears to be different from the action of the sulfonamide drugs which I mentioned earlier, since it is now known that para-aminobenzoic acid is a part of the folic acid molecule and that the sulfonamide drugs prevent the incorporation of para-aminobenzoic acid into the folic acid. Specific antagonists for folic acid may give the final answer to the relation of folic acid to the anti-pernicious-anemia factor.

The studies have not been limited to vitamins. Dyer has shown that ethionine is toxic for young rats maintained on a diet free from methionine and that the toxicity could be prevented by the addition of the latter. In all cases the relationship between the nutrition and the drug therapy is obvious, and I believe that future studies along this line will be most productive.

For several years we have been studying the possible relation of nutrition to resistance to virus infection, using mice and several viruses closely related to the virus of infantile paralysis. We have found that mice deficient in thiamine are almost completely resistant to paralysis produced by these viruses. In the presence of adequate thiamine the incidence of paralysis reaches approximately 100 per cent. Similar results have been obtained with riboflavin and pantothenic acid, although the differences have not been so striking. It has also been possible to increase the resistance by producing potassium and phosphorus deficiencies. Recently this work has been extended to the field of amino acids, and we find that mice deficient in tryptophane show less paralysis when infected with the virus than those receiving adequate quantities. Furthermore, a more severe tryptophane deficiency develops in infected mice than in uninoculated ones. This may indicate that the virus has a preference for certain amino acids. This is not surprising, since it is known that the virus multiplies rapidly and that it is composed largely of protein material. This logically suggests the possibility of using certain analogues of tryptophane to alter or modify the development of certain viruses. There are undoubtedly many difficulties and obstacles in a program of this kind, but even if practical applications do not come out of this work much fundamental knowledge must accumulate.

In conclusion it may be said that from the point of view of drug therapy a compound having positive nutritional effects should theoretically disappear from the list of useful drugs. If the compound is known and its content in foods can be estimated, the corresponding deficiency should be prevented through the use of natural or fortified food and the deficiency should never appear. However, from past experience it is obvious that optimum nutrition for all will never be obtained and that there will always be need for these specific compounds for clinical use. The main objection to the use of pure substances in nutritional deficiencies is the fact that unknown factors may be ignored. That is why for several years vitamin B complex preparations always contained some natural sources of nutrients. The availability of synthetic folic acid apparently does not completely eliminate this necessity, and it may be some time before the natural sources can completely be ignored.

Studies on the development of compounds having a negative nutritional effect are in their infancy, and it is impossible to predict the extent to which these compounds may eventually be used in the treatment of infectious diseases. Nevertheless it is apparent that the search for new agents for use in human therapy will in the future be based largely on studies with animals and micro-organisms. Work in the field of nutrition has done much to establish the metabolic similarity between all living cells, which is the basis for this new type of approach.

TUBULO-VASCULAR SYNDROME—Renal vasconstriction is a rather general reaction occurring whenever the efficiency or integrity of the circulation is threatened by cardiac injury or disease, skeletal trauma, hemorrhage, dehydration, and comas. Presumably, the immediate effect of this diversion of blood from the kidney is to make more of the low cardiac output available to vital areas—heart, brain, lungs, liver. So far so good. A few hours of oliguria or even anuria is not a catastrophe; and it is a fact that the kidney can safely stand complete interruption of its arterial blood supply for 20 or 30 minutes. But when the state of renal vasoconstriction and marked ischemia persists for 12 to 24 hours or longer, something apparently happens to the vitality of the tubular epithelium and a whole series of dysfunctions arise, with or without structural alterations, that may lead irreversibly to uremia and death even though the original injury to the body or to the circulation may already have been corrected. . . . Leiter, Louis, M.D., Renal Diseases: Some Facts and Problems, Annals of Internal Medicine, February 1948, Vol. 28:241.

V 13
1948

GONOCOCCIC MENINGITIS FIFTEEN YEARS AFTER URETHRITIS

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Gonococcic meningitis is looked on as a rare disease. In many text books it is not even included among the complications of gonorrhea. The first mention of it was possibly in 1805, when nervous manifestations were described in conjunction with gonorrhea.[1] It was not until 1879 that the gonococcus was discovered, and not until 1905 [2] that positive means of identification, such as the differential sugar reactions and the agglutination, agglutinin absorption and complement fixation tests, were introduced. In 1909 the review of the literature of this malady by Henderson and Ritchie [1] closed the era of purely clinical diagnosis and opened a new era of laboratory confirmation.

What then are the criteria necessary to establish the identity of the gonococcus? Birkhaug and Parlow [3] have stated that in addition to the morphologic and cultural characteristics of this organism, the only reliable criterion is either its fermentation of dextrose or one of its serologic reactions, such as agglutination, agglutinin absorption or complement fixation. Branham, Mitchell and Brainin [4] have rated the dependability of the laboratory procedures for the identification of the gonococcus as follows: 1. The cultural features and the type of colony are the most fundamental and typical differences. The gonococcus produces a delicate growth on blood agar, with small translucent convex colonies. 2. The fermentation of various sugars is typical in that dextrose is readily fermented but no other sugar is so affected. 3. The alkali solubility test is of value but is not an absolute criterion. In the test of Thomson as described by Pelouze [5] the gonococcus is, as a rule, instantly and completely dissolved, leaving a completely clear solution. Meningococci are partially dissolved, but the stroma remains, leaving an opalescent fluid. Micro-organisms such as streptococci and staphylococci are untouched in the dilution of alkali used. 4. Serologic methods of differentiation have not been satisfactory, as gonococci are often agglutinated by polyvalent antimeningococcus serum as well as by antigonococcus serum. Nearly all gonococci are agglutinated more strongly by type II antimeningococcus serum than by the other type serums, although some show considerable cross agglutination.

Since all cases of gonococcic meningitis prior to 1905 were diagnosed without benefit of laboratory confirmation, this date may reasonably be used as a starting point for any present day review of this disease. Since that time 40 cases have been reported. In some of these instances adequate proof of the diagnosis is lacking, and therefore these cases must be considered merely as possibly or probably gonococcic in origin. Such reports would include those of Wynn,[6] Prochaska,[7] Bieck,[8] Romback,[9] Henderson and Ritchie,[1] Morelli [10] and Lindenfeld.[11] There remain 24 patients,[12] including the present one, in regard to whom the diagnosis can be considered to have been adequately established.

Gonococcic meningitis occurs more commonly in young male adults and, as a rule, it is secondary to a genital infection. All age groups have been involved, including a newborn infant.[2] Branham and associates [4] reported 2 cases of simple, uncomplicated primary gonococcic meningitis without any recognizable focus of infection, and as far as could be determined, no known opportunity for infection. It is interesting that our patient had experienced no gross recurrence of his primary gonorrheal urethritis in fifteen years, yet his meningitis apparently originated from an old focus in the prostate gland.

The signs and symptoms of gonococcic meningitis are apparently indistinguishable from those of meningococcic meningitis; the presence of gonorrhea or a suggestive history often indicates the true nature of the disorder. From the point of view of the pathologist the two diseases are grossly similar. In several instances gonococcic meningitis appeared in the presence of gonorrheal arthritis.

Marvin and Wilkinson [12i] in their review of the literature in 1938 told of a mortality of 45 per cent; they reported the first case in which the patient was treated with a sulfanilamide. Undoubtedly with the present day use of penicillin and the sulfonamide compounds, the mortality rate should decline markedly.

Five hundred cultures of blood and spinal fluid were made by Branham and associates [4] in a search for the meningococcus, and 10 (2 per cent) were found to contain gonococci. Subsequently these authors reported 3 additional cases. This leads one to suspect that gonococcic meningitis is more frequent than is commonly believed.

REPORT OF A CASE

C. M., a white man aged 35, was admitted to the hospital on June 3, 1946 because of nausea and vomiting of three days' duration. He had been well until three days prior to admission, when he became dizzy and nauseated and had fever. Shortly thereafter he experienced chilliness, generalized muscular cramping, malaise and a severe frontal headache. Stiffness of the neck then appeared. All symptoms

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became more severe on the day of admission. The vomitus now became dark brown, and there was severe epigastric pain. Red spots appeared on his skin; these were generalized in distribution and were not accompanied by itching or other discomfort. His past history disclosed that he had contracted gonococcic urethritis at the age of 20 years and that following treatment there had been no recurrence. Since this infection, however, he had suffered occasional slight dysuria.

The patient was a thin white man who appeared to be acutely ill. The blood pressure was normal in both arms, and the temperature was normal. The pulse rate was 94 and the respirations 22 per minute. Petechiae, varying from bright red to brown, were present in the skin and the mucous membranes. No abnormalities of heart or lungs were found. Some generalized tenderness of the abdomen was noted, but no masses were felt. Examination of the genitalia and the rectum did not reveal any abnormalities. Opisthotonos was present, and flexion of the neck caused marked pain. A Brudzinski sign was observed. The deep reflexes were hyperactive on both sides, and there was a bilateral Kernig sign.

A lumbar puncture brought cloudy fluid, which exerted a pressure of 230 mm. of water. About 15 cc. of fluid was withdrawn, and in its place was injected 10,000 units of penicillin in 10 cc. of isotonic solution of sodium chloride. The spinal fluid showed 94,000 white cells per cubic millimeter, all of which were polymorphonuclear leukocytes. Smears of the fluid showed gram-negative intracellular diplococci. The total protein was 1.93 Gm. per hundred cubic centimeters. The sugar was less than 20 mg. per hundred cubic centimeters. The globulin was 4 plus. The Wassermann reaction was negative. The colloidal gold curve was 1355555555.

The urine on admission was normal except for the presence of albumin. The blood count on admission showed red cells 4,610,000, white cells 27,300, hemoglobin 90 per cent; the differential cell count showed 92 segmented forms and 8 lymphocytes. The Wassermann test was negative.

Because the persistent vomiting prevented adequate oral medication, 5 Gm. of sodium sulfadiazine was given intravenously in 1,000 cc. of an isotonic solution of sodium chloride containing dextrose in a concentration of 5 per cent. Fifty thousand units of penicillin was given intramuscularly, and subsequent injections of 30,000 units each were given every three hours. After the initial intravenous dose of sodium sulfadiazine, the patient was given orally 2 Gm. of sulfadiazine every four hours, to which was added an equal amount of sodium bicarbonate. Suitable supportive measures were also applied. Two days after admission the blood sulfadiazine level was 14.2 mg. per hundred cubic centimeters.

The patient remained afebrile and improved rapidly. Three days after admission, a second lumbar puncture was done, and an initial pressure of 290 mm. of water was observed. The slightly cloudy fluid was slowly removed until the pressure reached 100 mm. of water, at which time 15,000 units of penicillin was injected intrathecally. Examination of this fluid revealed 850 white cells per cubic millimeter, all of which were polymorphonuclear leukocytes. No organisms were seen on smears, and no growth appeared on the cultures. The sulfadiazine level of the spinal fluid was 6.5 mg. per hundred cubic centimeters. The use of this drug was stopped on the twelfth day, after a total of 133 Gm. had been administered. The use of penicillin was discontinued after 1,000,000 units had been administered. Recovery was uneventful, and apparently there were no residual effects.

Prostatic fluid obtained at this time by massage revealed extracellular gram-negative diplococci, but no organisms were obtained from cultures. This is not surprising, however, in view of the medication to which the patient had been subjected.

Because of the hematemesis and epigastric pain during the early part of the illness, appropriate roentgenograms were made. These did not reveal any abnormality of esophagus, stomach or duodenum.

The organism grown from the spinal fluid obtained at the first lumbar puncture was identified as the gonococcus. A blood agar plate was inoculated with fresh spinal fluid and incubated aerobically. A chocolate agar plate was inoculated with fresh spinal fluid and incubated in 10 per cent carbon dioxide. After twenty-four hours the blood agar plate showed no growth, and the chocolate agar plate revealed small, dewdrop-like colonies, which were found to be gram-negative diplococci. Maltose, sucrose and dextrose were inoculated with these organisms, and dextrose was the only sugar fermented after forty-eight hours under carbon dioxide. Several attempts to agglutinate the organism with types I, II, III and IV antimeningococcus serums were unsuccessful. A fresh culture of the organism was grown on chocolate agar in 10 per cent carbon dioxide, and the culture was then flooded with 10 per cent dimethyl-paraphenylenediamine hydrochloride. The colonies gave a positive oxidase reaction, turning pink and then black. These tests confirmed the diagnosis of gonococcic meningitis.

SUMMARY

Twenty-four cases of proved gonococcic meningitis are found described in medical literature, but it is probable that the disease occurs more frequently than this figure would indicate.

The disease occurs chiefly in young male adults of both the white and the Negro race, and is generally secondary to gonorrheal urethritis.

The criteria for the positive identification of gonococcus are presented.

A case of gonococcic meningitis, probably secondary to chronic gonococcic prostatitis, is reported.

V 13
1948

CLINICAL EVALUATION OF THE ANALGESIC METHADON

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A new synthetic analgesic, originally prepared by German chemists and known as drug 10820, was made available to this country following World War II. The original report was published by the U. S. Department of Commerce.[1] The Council on Pharmacy and Chemistry of the American Medical Association has given this compound the nonproprietary name of methadon.[2]

The compound is a white crystalline substance soluble in water and alcohol, but insoluble in ether, having the following formula: 6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride. The compound contains an asymmetric carbon atom and is supplied as the racemic mixture. It is quite possible that the *d*- and *l*- isomers may have different degrees of activity.

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Acknowledgment is made to the Abbott Laboratories, Ciba Pharmaceutical Products, Inc., Eli Lilly & Company, Lederle Laboratories, Inc., Parke, Davis & Company, G. D. Searle & Co. and the Winthrop Chemical Co., Inc., for research grants given to the regents of the University of Minnesota for studies in clinical pharmacology.

Dr. Cecil J. Watson, Professor of Medicine; Dr. Owen H. Wangensteen, Professor of Surgery; Dr. John L. McKelvey, Professor of Obstetrics and Gynecology; Dr. A. B. Baker, Professor of Neurology, and Dr. Ruth M. Boynton, Director, Students Health Service, at the University of Minnesota Hospitals generously used the analgesic methadon on their services and allowed me to study and observe their patients.

1. Kleiderer, E. C.; Rice, J. B.; Conquest, V., and Williams, J. H.: Report 981, U. S. Department of Commerce, Office of the Publication Board, Washington, D. C.
2. Smith, A. E.: Personal communication to the author.

A pharmacologic investigation was undertaken by Scott and Chen,[3] who reported that the drug had some of the characteristics of both morphine and meperidine hydrochloride ("demerol hydrochloride" N.N.R.) in animals. The effects on the nervous, circulatory and respiratory systems, as well as the side effects, were similar to those of morphine. Action on the intestinal tract consisted of a morphine-like short period of spasm followed by an antispasmodic effect equal to that produced by meperidine hydrochloride. No tolerance or addiction to the drug was found. Determination of the pain threshold by the Wolff-Hardy technic indicated that, weight for weight, methadon was a more potent analgesic than either morphine or meperidine.

Woods, Wyngaarden and Seevers[4] have studied the addiction potentialities in rhesus monkeys and have found that physical dependence and withdrawal symptoms do not occur after chronic administration of methadon. They also found no tolerance to the drug but rather an increased susceptibility.

Recent investigations have been carried out by Isbell, Wikler and co-workers,[5] who found that 2.5 mg. of methadon given subcutaneously raised the pain threshold (Wolff-Hardy technic) as much as 10 mg. of morphine. Doses of 5 mg. of methadon produced little or no effect on temperature, pulse rate, blood pressure and respiratory rate in man. Larger doses slowed the pulse and lowered the blood pressure. Doses of 20 to 30 mg. of the drug always produced narcosis and sedation. They[6] also observed the effects of methadon in former morphine addicts and found that the abstinence symptoms from morphine could be controlled with methadon. When methadon was withdrawn abruptly after prolonged administration, the abstinence syndromes were so mild that treatment was not necessary.

Kirchof and David[7] have studied this drug in 84 patients in doses ranging between 5 and 15 mg. and reported that the control of pain was adequate and side effects were minimal. They did not observe withdrawal symptoms, sedation or hypnosis.

Scott, Livingstone, Jacoby and Broberg[8] have given methadon preoperatively and have observed the drug to be inferior to morphine due to its lack of sedative properties. However, it was found to be an effective analgesic.

Scott, Kohlstaedt and Chen[9] have reported use of this analgesic in a series of 210 patients, with 72.9 per cent obtaining complete relief of pain. The incidence of side effects in their patients was minimal and relatively unimportant.

Gentling and Lundy[10] have used methadon in 106 patients with a variety of diseases and reported that all but 4 patients had satisfactory relief of pain.

In April 1946 clinical trials of the drug were instituted at the University of Minnesota Hospitals. Up to the present time methadon has been given to a total of 400 patients for relief of all types of pain. This group consists chiefly of adults, except for 10 children.

Approximately 85 per cent of the drug was obtained from the Eli Lilly Laboratories, Indianapolis, under the name of "dolophine." The rest of the drug was supplied by the Winthrop Chemical Co., Inc., as "adanon," by the Abbott Laboratories as "AN 148" and by Parke, Davis & Company as "diaminon."

TABLE 1.—*Analgesia Obtained*

Clinical Condition	No. of Patients	Degree of Relief: Minimal or None No.	%	Moderate or Good No.	%	Very Good or Complete No.	%
Postoperative	134	18	14	42	31	74	55
Cancers	50	8	16	18	36	24	48
Bone Pain	32	3	9	16	50	13	41
Labor	25	17	68	5	20	3	12
Dysmenorrhea	11			1	9	10	91
Cough	13			2	15	11	85
Brain lesions	27	1	4	12	44	14	52
Headache	19	8	42	5	26	6	32
Miscellaneous	89	14	16	24	27	51	57
Average percentage			19		29		52

TABLE 2.—*Comparison of Methadon with Morphine and Meperidine*

Dose of Methadon	No. of Patients	No. Preference Pts.	%	Methadon Preferred Pts.	%	Morphine (10 to 15 Mg.) Preferred Pts.	%	Meperidine (75 to 150 Mg.) Preferred Pts.	%
5 mg.	47	22	47	10	21	15	32		
7.5 and 10 mg.	43	25	58	11	26	7	16		
5 mg.	35	16	46	11	31			8	23
7.5 and 10 mg.	21	4	19	11	52			6	29

Some of the conditions for which it was used to alleviate pain were: postsurgical, primary and metastatic carcinoma, arthritis, herniated disk, thalamic pain, myalgia, neuritis, headache, ulcer of the leg, anginal pain, cholecystitis, common duct stone, dysmenorrhea, labor and gastric and duodenal ulcers.

The methods of administration were oral (as capsules, tablets and elixir), hypodermic and intravenous. Onset of action was two minutes when given intravenously, within fifteen or twenty minutes when given hypodermically, or when given orally as the elixir, and thirty minutes when given orally in capsules or tablets. By all routes of administration it was found that the average duration of action was from three to four hours, with many of the patients obtaining relief for as long as eight to twelve hours. The majority of patients received the drug hypodermically at three to four hour intervals as necessary. When continuous use of analgesics was indicated, the elixir was substituted successfully for hypodermic injection on

3. Scott, C. C., and Chen, K. K.: The Action of 1,1-Diphenyl-1-(Dimethylaminoisopropyl)-Butanone-2, a Potent Analgesic, J. Pharmacol. & Exper. Therap. **87:** 63 (May) 1946.
4. Woods, L. A.; Wyngaarden, J. B., and Seevers, M. H.: Addiction Potentialities of 1,1-Diphenyl-1-(B-Dimethylaminopropyl)-Butanone-2 Hydrochloride (Amidone) in the Monkey, Proc. Soc. Exper. Biol. & Med. **65:** 113 (May) 1947.
5. Isbell, H.; Wikler, A.; Eisenman, A. J., and Frank, K.: Effect of Single Doses of 10820 on Man, Federation Proc. **6:** 341 (March) 1947.
6. Isbell, H.; Eisenman, A. J.; Wikler, A.; Daingerfield, M., and Frank, K.: Treatment of the Morphine Abstinence Syndrome with 10820, Federation Proc. **6:** 340 (March) 1947.
7. Kirchof, A. C., and David, N.: Clinical Trial of a New Synthetic Heptanone Analgesic (Dolophine), West. J. Surg. **55:** 183 (March) 1947.
8. Scott, W. W.; Livingstone, H.; Jacoby, J. J., and Broberg, G. R.: Early Clinical Experience with Dolophine (No. 10820), Anesth. & Analg. **26:** 18 (Jan.-Feb.) 1947.
9. Scott, C. C.; Kohlstaedt, K. G., and Chen, K. K.: Comparison of the Pharmacologic Properties of Some New Analgesic Substances, Anesth. & Analg. **26:** 12 (Jan.-Feb.) 1947.
10. Gentling, A. A., and Lundy, J. S.: A New Analgesic, AN—148: Preliminary Report, Proc. Staff Meet., Mayo Clin. **22:** 249 (June 25) 1947.

the patient's discharge from the hospital. No appreciable difference in potency was found between hypodermic injection and the oral administration of the elixir. However, in equivalent amounts the capsules and tablets were found to be inferior to the hypodermic, intravenous and elixir forms of the drug, requiring almost twice the dose to produce the same effects.

Originally, 2.5 and 5 mg. doses of methadon were used. The 2.5 mg. doses relieved only the mildest pain, while 5 mg. doses relieved only moderately severe pain. The doses were therefore increased to 7.5 and 10 mg., which were adequate to relieve patients experiencing extremely severe pain. In 1 patient in the terminal phase of generalized leukemic reticuloendotheliosis, 15 and 20 mg. of the drug administered intravenously every two hours were necessary for the relief of excruciating bone pain. Methadon in doses of 10 mg., either hypodermically or intravenously, proved to be more effective than 15 mg. of morphine in this patient.

A summary of the number of patients, type of pain treated and degree of relief obtained is shown in table 1. All degrees of pain, all doses from 2.5 to 20 mg. and all routes of administration are included, although not indicated, in the tabulation.

Obstetric patients in labor received doses of 5 to 10 mg. without resulting cyanosis of the infant, but the analgesic effect was inferior to that of meperidine hydrochloride.

When incorporated in a syrup, the drug is effective in depressing the cough reflex and has been used by several patients in whom other medicaments had failed; however, the incidence of side effects is relatively high.

Morphine and meperidine hydrochloride were used alternately with methadon in 90 patients during the course of therapy for comparison of effects. In doses of 5 to 10 mg. methadon proved to be more effective than meperidine hydrochloride in any dosage from 75 to 150 mg. When effects of 5 mg. doses of methadon were compared with 10 to 15 mg. doses of morphine, there was a slight preference for morphine. However, 7.5 and 10 mg. doses of methadon were somewhat more effective than 10 and 15 mg. doses of morphine. It was found that the analgesic effect of 10 mg. of methadon was equal to that of 15 mg. of morphine or 150 mg. of meperidine hydrochloride and in many cases was superior. This observation was also made independently by Kohlstaedt [11] and his associates, both clinically and experimentally. A summary of the comparison of methadon with morphine and meperidine is shown in table 2.

TABLE 3.—*Incidence of Side Effects*

Clinical Condition	No. of Patients	Side Effects Pts.	Side Effects %	Nausea and Vomiting	Amnesia	Sedation	Dizziness	Dry Mouth	Headache	Euphoria	Miosis	Itching
Postoperative	134	5	4	1		4	1				1	
Cancers	50	2	5	1		1	1					
Bone Pain	32	2	8	2			1					1
Labor	25	8	32	4	2	2	1	2				
Dysmenorrhea	11	7	63	4		2			1	1		1
Cough	13	5	45	2		3	1					
Brain lesions	27	5	20			4						
Headache	19	6	32	4		2	2				2	
Miscellaneous	89	8	11	3		3	3					2

Sixty-seven side effects occurred in 52 patients; 13 per cent of patients had side effects.

Eighty-one per cent of the patients had adequate or complete relief of pain, and this figure would be increased to 86 per cent if the group of patients who received methadon for labor pains were excluded, since the drug has proved to be ineffective in this type of pain. Effects of methadon that were particularly notable were the minimal amount of sedation, the low incidence of psychologic phenomena, such as euphoria and clouding of mentality, and the presence of a relaxing effect. Most patients expressed pleasure in being able to carry on with normal activities even when receiving 10 mg. of the drug hypodermically every three hours.

It was possible to use methadon to relieve muscular spasm and pain in patients with bulbar and spinal poliomyelitis even when they were confined in respirators because of the minimal sedative effect. Doses of 5 mg., and occasionally 7.5 mg., were adequate and did not produce any respiratory difficulty. The effects of this drug were striking in these cases, since other narcotic analgesics or barbiturates caused severe respiratory depression.

Methadon was also used effectively to relieve headaches due to brain tumor, head injury, brain abscess and hemiplegia and headaches following encephalograms and ventriculograms without encountering any undesirable depressant effects.

Side effects were present in 13 per cent of the patients and included nausea and vomiting, sedation, euphoria, pinpoint pupils, amnesia, dry mouth, headache and itching, as noted in table 3. When divided into groups according to dosage it was found that the incidence of side effects was 13 per cent in the 232 patients that received 5 mg. of methadon, 12 per cent in the 104 that received 7.5 mg. and 22 per cent in the 57 patients that received 10 mg. It therefore appears that 5 and 7.5 mg. doses would be most satisfactory for general use from the standpoint of freedom from toxic reactions.

Nausea and vomiting occurred chiefly in ambulatory patients who took the drug in elixir form for dysmenorrhea and headaches. Hyperdermic administration of the drug for the same conditions produced this effect infrequently. The sedation produced was generally a slight drowsiness. However, in 2 patients over 60 years of age who had complicated postoperative courses, a dose of 7.5 mg. administered every four hours caused sufficient respiratory difficulty to warrant discontinuation of

11. Kohlstaedt, K. G.: Personal communication to the author.

V 13 1948

the drug. The relatively low incidence of euphoria may prove to be a handicap in severely depressed patients, although it was necessary to change to morphine for this reason in only 1 patient, who proved to be a difficult nursing problem because of his depression. Pupillary changes were noted only in 3 patients in whom miosis occurred. Dizziness occurred principally in ambulatory patients. Itching was severe in two patients, but was relieved by diphenhydraminehydrochloride ("benadryl hydrochloride" N.N.R.). It was not necessary to discontinue methadon in either of these patients, and both are continuing to take the drug with no recurrence of itching even though administration of diphenhydramine has been discontinued.

Prolonged administration of methadon at regular intervals up to twelve months did not cause associated constipation or change in bowel habits. There has also been no effect on the hemoglobin or white blood cell counts.

Development of tolerance occurred in some patients who were at first adequately relieved by a dosage of 7.5 mg. but later required 10 mg. It was also necessary to decrease the three to four hour interval between administrations to one to two hours. Most of these patients had generalized carcinomatosis, and an increasing severity of pain during the last few days of life may have been a factor.

Thus far there has been no evidence of addiction in the sense that physical dependence and withdrawal symptoms occur. Approximately 20 patients receiving methadon for two or three months had no withdrawal symptoms on abrupt discontinuation of treatment. Three patients who have been treated with the drug for one year have all been able to decrease dosage at will and to discontinue use for as long as two to six weeks without ill effects. It is believed, however, that this relatively small number of patients does not warrant a final statement concerning addiction.

It was possible to replace morphine, meperidine, "pantopon" (the total alkaloids of opium as soluble hydrochlorides) and dihydromorphinone with methadon in persons addicted to each of these drugs. The dose used and the frequency of administration depended on the amount of drug the addict was accustomed to taking. None experienced withdrawal symptoms during the time the narcotic was being withdrawn or after the termination of treatment with methadon.

Thus far contraindications to the use of this drug have not been encountered, and it has been used successfully in patients with idiosyncrasies to morphine and to meperidine. In patients with dysmenorrhea and headache the routine use of the elixir is not encouraged because of the high incidence of nausea and vomiting. In obstetric analgesia the results produced are not as satisfactory as those of meperidine.

SUMMARY

Methadon, a new synthetic analgesic, has been used clinically in various types of pain and has been compared with morphine and meperidine.

1. The drug has characteristics of both morphine and meperidine.
2. Oral use of the elixir is almost as effective as the hypodermic injection.
3. Ten mg. of methadon is as effective in relieving pain as 15 mg. of morphine or 150 mg. of meperidine.
4. Adequate or complete relief of pain occurred in 81 per cent of 400 patients.
5. Less sedation and euphoria occur with methadon than with morphine.
6. Side effects occurred in 13 per cent of patients.
7. Tolerance to the drug may develop.
8. Addiction has not been definitely established.

ENCEPHALITIS AS A CAUSATIVE FACTOR IN BEHAVIOR DISORDERS OF CHILDREN

An Analysis of Seventy-eight Cases

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The following report is of observations made on 78 children who were referred to the Child Guidance Home because of personality difficulties and behavior disorders which were found to be causally related to a previous attack of encephalitis. At this point a word about the procedure which has been employed at the Child Guidance Home since its inception in 1920 is appropriate. Every child admitted for observation is studied from the psychobiologic point of view, which entails a knowledge and understanding of all the factors, physical, psychiatric, psychologic and sociologic, which may be involved in a given case; in other words, a study of the total situation, a procedure which has been recently emphasized by various authors.[1] It was only after the evaluation of the findings made from such an extensive study that the aforementioned relationship in the 78 cases was made. Furthermore, the excellent facilities of the institution for follow-up permitted a continuous dynamic study, which in some cases covered more than twenty-five years. This is the third report based on this continuing study, the first two being concerned with only 50 cases. Excerpts from these two papers are embodied in this report for the sake of completeness.

Among the conclusions reached as the result of the first two studies were the following:

> Encephalitis following acute virus or bacterial infections or cerebral trauma early in childhood may lead, in addition to structural cerebral changes, to behavioral and personality disturbances of such gravity as to prevent normal adjustment to life; this, despite the fact that the intellect may be unimpaired . . . . Encephalitis illustrates better than any other disease that changes in the structure of the brain may lead to changes in function. Since the encephalitic process may attack any part of the brain, the disorganization of function will correspond to the level or levels of the brain stem involved. Hence, vegetative, motor or intellectual dysfunction either alone or in combination may be present.[2]

Read before the Section on Pediatrics at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N. J. June 11, 1947.

From the Child Guidance Home of the Jewish Hospital.

1. Wilson, G. and Rupp, C., Jr.: The Practice of Neurology, J. A. M. A. **133**: 509 (Feb. 22) 1947. Burlingame, C. C.: Psychiatric Sense and Nonsense, J. A. M. A. **133**: 971 (April 5) 1947.
2. Greenebaum, J. V.; Lurie, L. A.; Leichtentritt, B., and Rosenthal, F. M.: Effects of Encephalitis Occurring During Childhood on Behavior and Personality, Ohio State M. J. **41**: 1015 (Nov.) 1945. Lurie, L. A.; Greenebaum, J. V.; Leichtentritt, B., and Rosenthal, Florence M.: Late Results Noted in Children Presenting Postencephalitic Behavior, Am. J. Psychiatry, **104**: 171 (Sept.) 1947.

These conclusions have been strengthened by the study during the past five years of the additional 28 cases reported in this series.

Of the 78 children constituting this series, 61 were boys and 17 were girls, and their ages at the time they were referred for study ranged from 4 to 19 years (fig. 1). The general proportion of boys to girls studied at the Child Guidance Home has been in the ratio of 2 to 1. In this series the ratio is almost 4½ to 1. This would appear to agree with the findings of other investigators; namely, that boys appear to be more apt to show postencephalitic type of behavior and personality changes than girls. The 78 children were taken from an unselected series of 2,700 children presenting all types of behavior disorders. This gives an incidence of 2.85 per cent.

According to figure 2, approximately 50 per cent

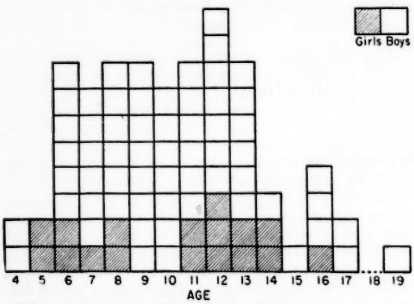

Fig. 1.—Distribution according to age and sex.

of the patients were admitted for study during the years 1940 to 1946. The exact age of onset of the disease was unknown in 12 cases. Eighty per cent of the known cases fall in the age range of 5 months to 7 years. The remainder are scattered over the remaining 11 years (fig. 3). Both these findings correspond to those of a study of acute encephalitis made at the Children's Hospital and the Cincinnati General Hospital.[3] In a series of 113 cases of acute encephalitis observed between the years 1919 and 1947, 91, or over 80 per cent, also occurred in children under the age of 7 and 98, or 87 per cent, similarly occurred between the years 1940 and 1946.

Table 1 shows the types of encephalitis as ascertained from the medical histories. From this it will be seen that the majority (37) were of the virus type, 29 of the toxic type and 12 of the traumatic type.

The age range of onset of the behavior difficulty or personality change showed a rather wide scatter with two peaks, one 3 to 4 years and the other 10 to 11 years. The age of onset of the problem was not learned in 6 cases (fig. 4).

In 64 cases the interval in years between the onset of the illness and the time of the onset of the problem was as follows: no interval or immediate onset in 40 cases; one year interval in 14 cases; two year interval in 3 cases; three year interval in 2 cases; five year interval in 2 cases; eight year interval in 2 cases, and nine year interval in 1 case. In 14 cases, the exact time of onset of the problem could not be determined.

It is interesting to note that although behavior disorders and personality changes were noted immediately after the onset of the disease in most

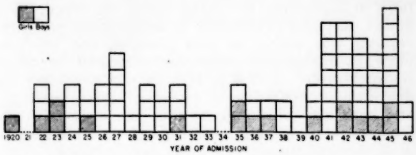

Fig. 2.—Distribution of cases of encephalitis according to years of admission to the Child Guidance Home, 1920 to 1946.

of the cases, not one of the 78 patients was referred for study during the acute phase of the illness. All were referred at much later dates when persistent behavioral or personality difficulties made them severe problems to their parents or to their communities.

The majority of the children were referred for more than one type of behavior disorder. These ranged from such simple behavior complaints as incorrigibility, truancy and temper tantrums to the more severe types of antisocial behavior in the form of sexual misconduct, stealing and other delinquent and criminal acts. In addition some presented serious abnormal types of behavior such as extreme restlessness, delusions and hallucinations.

NEUROLOGIC AND ELECTROENCEPHALOGRAPHIC ABNORMALITIES

Neurologic abnormalities were noted in all but 21 cases. In 38 cases there were pyramidal signs; in 20 cases, extrapyramidal signs, and in 16 cases,

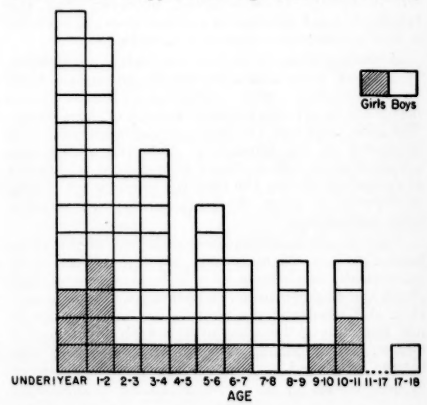

Fig. 3.—Age range of onset of disease.

ocular symptoms. Three children had persistent petit mal attacks and 6 suffered from grand mal seizures. Seven children showed the typical signs of parkinsonism.

3. Stine, F. A.: Personal communication to the authors.

4. These interpretations were made by Drs. G. Maltby, G. Engel and H. Lederer of the Cincinnati General Hospital.

V 13
1948

Electroencephalograms were made in 15 cases. In 6 cases, the tracings were normal; in 8 abnormal, and in 1 case questionable. The abnormal tracings were of two types: (1) typical tracing of epilepsy and (2) tracings which showed generalized cerebral dysrhythmia characteristic of psychomotor disturbances.[4] In 3 of 4 cases with no neurologic abnormalities noted, the electroencephalographic tracings were normal. In 6 cases with observed neurologic abnormalities, the tracings were normal in 5 cases and questionable in 1 case. In the remaining 5 cases, both the neurologic findings and the electroencephalographic tracings were abnormal.

According to the results of the psychometric tests made at the time of their admission to the Child Guidance Home, 3 children in this series rated superior, 26 were of average intelligence, 17 were subaverage, 14 rated borderline and only 18 were feebleminded (table 2). Psychometric examinations were repeated in 47 cases several years after the children's dismissal from the Child Guidance Home. The intelligence quotients remained the same in 9 cases, improved in 1 case and deteriorated in 37 cases.

TABLE 1.—*Types of Encephalitis*

I. Virus type	
1. Polioencephalitis	5
2. Lethargic encephalitis	7
3. Influenza encephalitis	7
4. Measles encephalitis	8
5. Chickenpox encephalitis	1
6. Virus encephalitis of unknown origin	9
Total	37
II. Toxic type	
1. Diphtheritic encephalitis	2
2. Scarlet fever encephalitis	2
3. Pneumonia encephalitis	4
4. Whooping cough encephalitis	15
5. Meningoencephalitis	1
6. Other toxic conditions of unknown origin	5
Total	29
III. Traumatic type	
Total	12
	78

TABLE 2.—*Psychometric Tests*

Intelligence Quotients	Rating	Number
110 and above	Superior	3
90 - 110	Average	26
80 - 90	Subaverage	17
70 - 80	Borderline cases of probable mental defect	14
70 and below	Feebleminded	18

TABLE 3.— *Patterns of Behavior*

Type	Number
Simple behavioral	26
Psychopathic	36
Psychotic	16
Total	78

At the Child Guidance Home every child is typed on a special personality chart. Sixty-one of the children (approximately 80 per cent) in this series received a uniform personality rating which was fairly distinctive and characteristic. In general these children were suspicious, impulsive, egocentric and selfish. They exhibited violent temper tantrums and were extremely obstinate. Emotional instability, unreliability and lack of initiative were outstanding shortcomings. They lacked ability to concentrate and showed little or no self control, their behavior being extremely unpredictable.

The remaining 17 children in the series received a nondescript personality rating in which the various characteristics enumerated were not uniformly present.

Rorschach tests were made in 10 of the last of 28 cases studied. The results were for the most part in agreement with the general characterization of the postencephalitic type of personality structure as shown in the cases cited. This will be the subject of a later paper.

TYPES OF ABNORMAL BEHAVIOR

The abnormal patterns of behavior which these children exhibited can be readily divided into three groups: (1) simple behavioral disturbances; (2) psychopathic behavior, and (3) psychotic behavior. Of the 78 cases, 26 presented simple behavioral difficulties, 36 showed psychopathic type of behavior and 16 showed psychotic type of behavior (table 3).

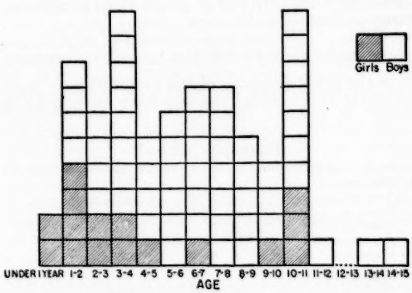

Fig. 4.—Age range of onset of problem.

Group 1.—The children who came under the simple behavioral classification were restless and hyperactive and exhibited temper tantrums. They were noisy and domineering. Aggressiveness was an outstanding symptom. Stealing, lying and running away were frequent occurrences. Enuresis was often present. These children were extremely difficult to control.

Group 2.—Of those who presented psychopathic types of behavior, some were phlegmatic and apathetic and apparently indifferent to what was going on around them. They gave the impression of being dull intellectually, even though their intelligence quotients, as shown on the psychometric tests, were normal or above normal. They were asocial and made little effort to enter into group activities. They concentrated poorly and were either unable or unwilling to carry out instructions. The majority of this group, however, were extremely restless and hyperactive, and lacked ability to concentrate.

In many instances, they were vicious, cruel and apparently deliberately abusive to other children. The unpredictability of their behavior was outstanding. Night terrors, sleep walking, breathing difficulties, food fads and habit tics were frequent complicating symptoms.

Group 3.—Those children who were classified as psychotic showed severe disorganization of cerebral function. They were careless of their personal appearance and were slovenly in all their habits. Moodiness, crying spells and irrelevant talk were often noted. Outbursts of screaming and causeless laughter were also often present. Occasionally hallucinatory phenomena were in evidence. These children had no insight whatsoever into their condition. It was impossible to control them, and they became violent when thwarted. Some refused to wash, bathe or change their clothes, often insisting on going to bed in the clothes which they had worn during the day. Rapport with them was impossible. Their behavior was comparable in many respects to that of the hypomanic. Some of these cases had been diagnosed as schizophrenia.

Case reports illustrating each of these 3 groups are appended.

As has been stated, the children in this study have been followed for periods ranging from three to twenty-six years, the majority having been followed for more than fifteen years. Their present age range is from 10 to 43 years.

COMPARISON OF ADJUSTED AND UNADJUSTED GROUPS

In the great majority of the cases, various types of social and medical therapy have been tried in order to bring about a social adjustment or at least an amelioration of the symptoms. The results have been highly disappointing. Only 12 of the 78 patients are at present adjusted. In the adjusted group there were 9 boys and 3 girls. Eight had had the virus type, 3 the toxic and 1 the traumatic type of encephalitis.

Personality Chart *

1.	Temperament				
	Trustful	A	B	*C*	Suspicious
	Impulsive	*A*	B	C	Phlegmatic
	Sanguine	A	*B*	C	Depressed
	Non-egocentric	A	B	*C*	Egocentric
	Generous	A	B	*C*	Selfish
2.	Temper				
	Placid	A	B	*C*	Violent
3.	Tractable	A	B	*C*	Obstinate
	Impressionable	A	B	*C*	Unimpressionable
4.	Intellectually				Intellectually
	Honest	A	B	C	Dishonest
5.	Mentally				Mentally
	Alert	A	B	C	Dull
6.	Emotionally				Emotionally
	Stable	A	B	*C*	Unstable
7.	Character traits				
	Reliable	A	B	*C*	Unreliable
	Original	A	B	*C*	Imitative
	Leader	A	B	*C*	Follower
	Concentration	A	B	*C*	Lack of concentration
	Self-control	A	B	*C*	Lack of self-control

* For convenience in typesetting the letters which might be circled in pen and ink in an actual form are set in italics.

Comparison of the adjusted and unadjusted groups reveals some rather significant differences. In the unadjusted group (66) there is a preponderance of the toxic and traumatic forms of encephalitis. Severe neurologic sequelae were also more prevalent, convulsive seizures having developed in 8 of the children in this group in contrast to but 1 in the adjusted group.

A noticeable and significant difference between the two groups was the much greater number of children in the unadjusted group who showed intellectual deterioration; specifically, 34 (51 per cent) in the unadjusted group compared with only 2 (16 per cent) in the adjusted group.

Another significant difference was the proportionately larger number of children in the unadjusted group who have the typical personality structure characteristic of the postencephalitic. There were 54 (82 per cent) in the unadjusted group in contrast to 7 (58 per cent) in the adjusted group.

There was also some difference in the two groups with respect to types or patterns of behavior. The number of children exhibiting psychopathic and psychotic behavior was far greater in the unadjusted group, 70 per cent compared to 58 per cent in the adjusted group. This was especially noticeable in the number showing psychotic reactions.

These differences, therefore, furnish a possible prognostic basis for the determination of the ability of the child showing postencephalitic behavior to adjust socially.

COMMENT

Our series of 78 cases was taken from a group of 2,700 children showing all types of behavior disorders, which gives an incidence of approximately 2.9 per cent. This is a significant percentage. From our experience with postencephalitic type of behavior we feel that the disease, as a complication of acute infectious and contagious diseases of children, is frequently overlooked. One of the reasons for this may be the fact that the neurologic examination often fails to disclose any abnormality. Another reason, and probably a more potent one, is the fact that in the great majority of cases there is no history of an attack of encephalitis. It is only when the medical history of the child as well as his behavioral reactions are carefully scrutinized and evaluated from the standpoint of a possible encephalitic episode, complicating an acute infectious or contagious disease occurring in the first decade of life, that the condition becomes apparent. We are in agreement with Bender [5] that "the diagnostic criteria for encephalopathic behavior disorders are now considerable. Even without the history of a specific etiological factor or evidence of the specific (neuro)pathology, the diagnostic methods which may be applied to fields of behavior are sufficient to establish a diagnosis."

One must consider the possibility of postencephalitic type of behavior when confronted with a child who is extremely hyperactive, restless and destructive, has a short attention span, is highly distractible, lacks self control and whose actions are extremely unpredictable.

5. Bender, quoted by Neal, J. B.: Encephalitis: A Clinical Study, New York, Grune & Stratton, Inc., 1942, pp. 379-380.

V 13 1948

Furthermore, the longer a case is followed, the more characteristic the clinical picture becomes. Often where the condition was originally only suspected, reexamination later easily established the correctness of the tentative diagnosis. As time goes on the pattern of behavior and characteristic personality changes become more clearcut and pathognomonic. The first 2 cases cited in this report illustrate this point clearly. If these facts are borne in mind, many more cases of uncorrectable behavior disorders and irreversible personality changes will be found to fall into this category.

SUMMARY AND CONCLUSIONS

A report on the study of 78 children presenting behavior disorders and personality changes following an attack of encephalitis is presented.

The cases were followed for periods ranging from four to twenty-six years, the majority having been followed for more than fifteen years.

Of the 78 children constituting this series, 61 were boys and 17 were girls, a ratio of more than 4½ to 1. This tends to bear out the findings of other investigators that boys are more apt to show postencephalitic type of behavior and personality changes than girls.

The 78 children comprising this series were taken from an unselected series of 2,700 children studied as inpatients at the Child Guidance Home, who presented all types of behavior disorders. This represents an incidence of approximately 2.9 per cent and indicates that the condition is by no means rare. The diagnosis will be made with even greater frequency once it is recognized that it can be made on the basis of the characteristic behavior reactions and personality changes even without a specific history of a previous attack of encephalitis or the presence of neuropathologic changes.

The age range of onset was in the first decade of life in 60 of the cases, 43 occurring before the age of 5 years. Furthermore, the younger the patient when affected by the disease, the greater the likelihood of psychiatric sequelae.

The types of encephalitis as ascertained from the medical histories showed that the majority (37) were of the virus type, 29 of the toxic type and 12 of the traumatic type.

In the great majority of the cases the behavior difficulty or personality change was noted immediately after the attack of encephalitis.

The majority of the children were referred for multiple behavior problems. These covered the usual range of problems ordinarily studied at child guidance clinics.

The abnormal patterns of behavior which these children exhibited could be readily divided into three groups: (1) simple behavioral disturbances, (2) psychopathic behavior and (3) psychotic behavior.

When these children were first studied, 14 were found to be feebleminded and 7 rated borderline. The remainder (57) were either of average or of superior intelligence.

Forty-seven of the children were retested several years later. The intelligence quotients remained the same in 9 cases, improved in 1 case and deteriorated in 37 cases. The frequency of intellectual deterioration is worthy of note as it seems to refute the prevailing belief that the most severe and lasting damage is in the emotional sphere in contrast to the preservation of the intellect.

Neurologic abnormalities were noted in all but 22 cases. These were of both the pyramidal and the extrapyramidal type. Ocular symptoms were present in 16 cases. Three children had petit mal attacks and six suffered from grand mal seizures. Seven children showed symptoms of parkinsonism.

Electroencephalograms were made in 15 cases, of which 8 were abnormal. The abnormal tracings were of two types: (1) tracings typical of epilepsy and (2) tracings showing generalized cerebral dysrhythmia, characteristic of psychomotor disturbances.

Sixty-one (80 per cent) of the children in this series had a uniform and characteristic personality makeup. In general, lack of inhibition, restlessness, impulsiveness, extreme distractibility and unpredictibility of behavior were the dominant personality traits.

The prognosis from the standpoint of social adjustment is poor. Only 12 children in this series of 78 have made a fair social adjustment; this despite the application in the majority of cases of the best available medical, psychiatric and social therapeutic technics.

The failure of social therapy and psychotherapy in these cases cannot be attributed to faulty social or psychiatric technics. Rather, such failure indicates that the problem of the child presenting postencephalitic behavior disorders or personality changes is not solely one of psychopathology and psychodynamics. The psychopathologic symptoms are primarily the results of the neuropathologic changes, and it is our present inability to correct the latter which accounts for the failure of treatment. These cases illustrate pointedly the relation of structure to function in human behavior. For this reason, it is essential for all who are interested in behavior disorders of children, particularly pediatricians, to use the classic psychobiologic approach when studying problem children.

REPORTS OF CASES

CASE 1.—Billy, aged 10, was admitted to the Child Guidance Home for the first time in June 1941 because he was unable to adjust either at home or at school. He felt that every one picked on him, and in turn his classmates complained that he hit, pinched and bit them.

According to the social history, the father and mother were incompatible. The father drank heavily and consorted with other women. The mother appeared to be a rather stable person, who considered herself responsible for the support of her family because of her husband's incompetence. Her attitude toward the child was one of overprotectiveness, and toward her husband one of resigned indifference. She worked during the day and the father worked at night. Consequently, the boy had little supervision and little association with his parents. The father felt that Billy's problems were entirely due to the family situation. He stated that he, the father, was the only one to whom the boy had ever been really attached. The constant friction in the home made for a tense, unhappy situation. The boy received neither love nor affection from his parents and felt insecure. Of significance in the boy's medical history was the fact that he had had a severe attack of measles early in infancy which was complicated by bilateral otitis media.

At the Child Guidance Home the physical and neurologic examinations disclosed no significant abnormality. The boy had an intelligence quotient of 121. He was hyperactive and restless, and concentrated poorly. He was un-

able to get along with the other children and did not hesitate to throw rocks at them without any apparent cause. He was a poor sport and a coward. The children heartily disliked him and kept out of his way as much as possible. In psychiatric interviews the boy talked quite freely. He told about his home situation and said that he had been moved around a great deal. He admitted that he could not get along with children at school and said that sometimes they called him "sissy." This was because he would cry and run away if he found that he was getting the worst of any situation. He thought it might help if he were bigger and stronger and better able to stand up for himself. He stated that he did not want to live with either one of his parents alone. What he really wanted was to have a normal home with both parents present. He was well aware of the friction between his parents and was unhappy about this. The boy appeared to have fair insight into his condition. His lack of security and feeling of inferiority were evident.

The diagnosis at this time was that most of Billy's difficulties were due to faulty parent-child relationships. It was recommended that the boy be placed in a good boarding home where he would receive the love and affection of which he had been deprived, and where he could develop a feeling of security. The recommendation was carried out. However, despite intensive social therapy, the boy did not adjust in this and in other homes in which he was subsequently placed. He was then placed in a Children's Home, where he also failed to adjust. The Children's Home asked that the boy be readmitted to the Child Guidance Home for further study. The physical and neurologic findings at this time were approximately the same as they had been at the time of his previous study. His intelligence quotient was still 121 and his social quotient 103. Billy's behavior reactions followed the same pattern as they had on previous study except that they were more extreme. He was provocative, restless and aggressive, had a short attention span, was undependable, destructive and slovenly about his person. The boy stole and tried to lie out of every situation. A Rorschach test made for the first time revealed strong evidence of cerebral damage. His rating on the personality chart was characteristic of the postencephalitic. The electroencephalographic tracing, however, was normal. On the basis of the present observations and the medical history of a severe attack of measles early in infancy complicated by a bilateral otitis media, it was felt that the boy was presenting a postencephalitic type of behavior. The unwholesome home situation and the faulty parent-child relationships were also contributory but only in the sense that they had determined the trend or direction of the antisocial behavior. A recommendation for special institutional placement was made, but this could not be carried out as there was none available. Billy was therefore returned to Children's Home and placed in a cottage with older boys. There he again presented so many difficulties that the Children's Home refused to keep him. The only other available placement was a school for delinquent boys, where he was placed. There he proved to be most difficult. He ran away repeatedly, and after a short time had to be taken home by his mother. Then the neighbors began to complain and reported that he had stolen, pulled the main light switches in apartment buildings, and rung apartment doorbells late at night. They became so upset by his behavior that they went to court, demanding that drastic measures be taken. His teachers also stated that he was the worst problem they had ever encountered. In court, the mother promised to send the boy to a military school. After a brief stay there, the military school refused to keep him. The child was again brought before the court, and at the court's request he was readmitted once more to the Child Guidance Home for further study. At this time the neurologic examination showed some positive findings in the form of right internal strabismus with bilateral nystagmus, general muscle weakness with beginning atrophy of the muscles of the right forearm, and absent abdominal reflexes. The boy's intelligence quotient had dropped to 108. His behavior at the Home was extremely belligerent and he was abusive to the other children. He ran away several times and proved to be a nonconformist in every way. Psychiatric interviews were not very productive, as it was difficult to make satisfactory rapport with him. He bragged about his escapades and stated constantly that he had done nothing wrong and that every one else was to blame for his difficulties. Although he had been in many serious difficulties he minimized these and refused to admit that he had committed any wrong.

All who observed the boy felt that he was potentially dangerous and that in order to protect society it was necessary to institutionalize him. The only available placement was a hospital for the mentally ill, where he was admitted late in 1945 at the age of 14.

Comment.—This case illustrates the insidious nature of the disease in a boy whose behavioral difficulties at first appeared to be due entirely to faulty personal and interpersonal family relationships. However, on repeated examinations made over a period of years, it became apparent that his continued antisocial behavior was on an organic basis. This was first suggested by the interpretation of the Rorschach test. Furthermore, despite the fact that there was no history of an attack of encephalitis, the history of a severe attack of measles complicated by bilateral otitis media plus neuropathologic findings and the distinctive pattern of the boy's behavioral reactions warranted the diagnosis of postencephalitic behavior disorder. Admittedly, he is not properly placed in a hospital for the insane, as he never manifested any psychotic symptoms but merely uncontrollable antisocial behavior.

Case 2.—William, a white boy aged 13, was admitted to the Child Guidance Home in January 1930. The reason for his referral was that he had been involved in petty thefts and truancy for a long time. The social history revealed that his delivery had been instrumental, the mother dying in childbirth. The father was an alcoholic addict, and was killed by a train when William was 2 years of age. At first he was cared for by maternal aunts, and later he was boarded out. There was little material available regarding his early developmental history. It was noted, however, that the boy had suffered from various acute infectious diseases in infancy and early childhood with chronic involvement of the middle ear.

The physical examination made at the Child Guidance Home revealed no significant abnormality except for bilateral otitis media, with a loss of hearing of approximately 50 per cent in both ears. In the neurologic examination there were many positive findings in the form of unequal pupils and pyramidal tract signs. His intelligence quotient was 109.

At the Home, William proved to be a friendly boy who was liked by every one because of his frankness and willingness to be of service. It was noted that he was emotionally unstable, was socially immature and showed a strong feeling of insecurity. He was unable to carry out his good resolutions, although he apparently tried hard. He composed well, was a good musician and a leader in the club activities. He loved the Child Guidance Home and begged to be allowed to remain permanently. The boy talked freely and willingly in psychiatric interviews. He made good rapport with the psychiatrist and social workers. He appeared to have some insight into his condition. He admitted that he was weak willed, had many fears and always needed some one on whom he could lean. New experiences particularly frightened him. At this time it was felt that despite the fact that the boy was suffering from an organic involvement of the central nervous system of unknown origin, the unfortunate early conditioning had made the boy antisocial. It was therefore recommended that he be placed in a school where he would be under strict disci-

V 13
1948

plinary care and at the same time would receive psychotherapy. This recommendation was not carried out, and he remained with the aunt with whom he had been living. However, his truancy from school became such a problem that, at the insistence of the Attendance Department, the aunt placed him in a private military school where he remained for some time. Returning to his aunt for his summer vacation, he immediately got into trouble. He was charged with stealing, attacking a 5 year old girl, and driving a stolen car to a far distant city. He was then cited to court. Before he could be tried, the aunt returned him to the military school, but he ran away almost immediately, returning to Cincinnati, where he lived at several different hotels, giving fictitious names and leaving the hotels without paying. Again the boy was brought into court and referred to the Child Guidance Home for another period of observation.

Here it was noted that with the exception of the chronic otitis media, which had become worse, the results of all the physical examinations were essentially the same as on the first examination. The boy was still friendly and gregarious. However, he concentrated poorly, was unreliable and irresponsible. In psychiatric interviews, the boy's extreme immaturity was apparent; likewise, his poor concentration and ability to follow through. He admitted being weak willed and said that he readily followed any leader and so became involved in trouble. He stated that he was more restless than he had ever been and just wanted to run away from everything. Everybody and everything irritated him and he felt at times that he could not control himself. In one interview he said, "I'm afraid of the beginning of everything and afraid I can't do it. I like people after I'm with them and I get along with them. I'm unhappy. I don't like being on my own and I always get into trouble where I am." At this time the diagnosis was that the boy's behavior problems were due in part to an organic brain involvement probably as a result of some acute infectious disease, which had been complicated with encephalitis. The recommendation for custodial care in a special kind of institution, equipped to care for cases of that type for life, was recommended.

Again the recommendation was not carried out. Shortly thereafter, word was received that the boy had been arrested in Los Angeles, where he was committed to the Preston State School. Later in the year, William returned to Cincinnati. Following this, his aunt again placed him in a military school from which he promptly ran away.

William's history from that time on was a repetition of what had gone on before. He refused to stay in any one place, held jobs for just a few days, incurred debts, stole and burglarized. During the succeeding years, he was in the city workhouse, the boys' industrial school (state reformatory) and federal reformatory, where he is at present.

Comment.—When first seen at the age of 13, the diagnosis of postencephalitic behavior disturbance was not made in spite of neurologic findings and the presence of a chronic discharging ear. However, subsequent observation of the boy's behavior proved that the organic brain changes, encephalitic in nature, were basically responsible for his intractable and irreversible psychopathic behavior. Obviously incarceration in a reformatory is not the proper placement for a sick boy.

CASE 3.—Roy was admitted to the Child Guidance Home in February 1927, at the age of 13 years. It was stated that the boy had been a behavior problem for two and one-half years. The social history revealed that the father had been in poor health for many years and that the mother was nervous because of worry over her son's conduct. She helped support the family by conducting a small notion store. They had been independent until just recently, when they were forced to ask for financial assistance from a local social agency. There were 4 siblings, 3 boys and 1 girl, all in good health and all doing well at school. They presented no behavior problems. The developmental history showed that Roy's birth and early development had been normal. He had had chickenpox, measles and whooping cough. The ages at which he contracted these were not stated. The boy had an attack of acute epidemic encephalitis at 9 years of age.

At the Child Guidance Home the physical examination disclosed no significant abnormality, but there were positive neurologic findings in the form of pyramidal tract changes. The boy had an intelligence quotient of 122. From the moment he entered the Child Guidance Home it was noted that he was extremely difficult to control. He was impulsive, egocentric, depressed and suspicious. He exhibited violent temper tantrums during which he was unmanageable. His emotional instability was pronounced. The children obviously annoyed him and he did not hesitate to bite pieces out of their arms and legs when he became angry. There was no one with whom he could get along. He was extremely irritable and a serious sex problem. He ran away five and six times a day. There was no way of appealing to him or obtaining his cooperation. He did as he pleased and did not hesitate to destroy or injure anything or any one in his path. He had unusual physical strength and on one occasion tore a tie off of one of the children. In forcibly removing the tie he almost choked the boy. On the other hand, there were times when Roy appeared to be tractable and affectionate. At such times he would put his arms around any one at the Home and act in a tender and loving manner, but a moment later his mood would change and he would try to injure the object of his former affection. Such bizarre behavior as plucking hair from a child's head or sticking another with pins was of frequent occurrence. He could not be left alone with the other children, and because of his unusual physical strength no adult person at the Home was able to handle him alone. The children were in mortal terror of him. In psychiatric interviews, contacts were on an extremely superficial level because of the boy's apprehensiveness, antagonism and unwillingness or inability to respond. Attempts to reassure him and to get him into a more responsive frame of mind were unsuccessful. In most of the interviews he refused to answer at all and would sit with his head in his lap. Occasionally he spoke about his family. He was bothered about the poor economic conditions in his home. He felt that his mother did not have enough money to take care of the family properly. He showed many fears, particularly of the laboratory tests. There was no evidence of delusions or hallucinations.

It was felt that the boy had had an attack of lethargic encephalitis with resultant psychiatric disturbances, principally in the sphere of volition. It was recommended that he be institutionalized. The parents were both ununderstanding and uncooperative, and made no attempt to carry out the recommendation. A year later the mother reported that the boy had been committed to the boys' industrial school (a state correctional institution) as a result of conviction on a charge of assault and battery. The boy's record at the industrial school was bad. He did not adjust in any way. He was paroled in March 1929 and returned to his home. A short time later he was arrested and sent to a state hospital for the mentally ill, where the same diagnosis as that given at the Child Guidance Home was made. Later in the year, another report from the hospital stated that he had become much more difficult, was quarreling with the other patients, attacking them and threatening every one with assault. In October 1931, the state hospital reported that Roy was home on trial visit. He was attending classes in high school. However, after being home for eight months, he had to be returned to the hospital because the family could not control him. Each year Roy's behavior has become more difficult. In January 1946, at the age of 32, he was still in the state hospital, where it was reported that his behavior was both bizarre and unpredictable. His intelligence quotient was still 122.

Comment.—This case illustrates the psychotic sequelae of lethargic encephalitis. In this instance there has been no intellectual deterioration even

though the condition has existed approximately twenty years.

ABSTRACT OF DISCUSSION

DR. CHARLES BRADLEY, East Providence, R. I.: The essayists' study originates from a Child Guidance Center fully staffed for studies of this nature. Their observations form a record of behavior patterns following encephalitis in children whom they had not known before the infection. Nevertheless, they are able to discern clearly certain personality characteristics varying in intensity without history of such previous behavior. My observations in connection with the Child Guidance Clinic and with a large contagious diseases hospital are similar to those of the essayists, and I am much disturbed because of inadequate facilities available for the care of hopelessly damaged children, as well as by the dearth of well trained child psychiatrists. The pediatrician is not equipped by training or mode of practice to undertake similar studies. However, to him should fall the task of early diagnosis. He is familiar with the personality patterns of his little patients and can be alert to changes following infection. He needs to be familiar with the total environment in which each of his patients lives and to have an understanding of adverse environmental pressures to which each may be subjected. Such knowledge would help immeasurably in differentiating between emotional and infectional trauma. But, more important, he needs to give attention to the possibilities of preventive measures. A total number of virus and bacterial infections seen by the pediatrician is great, and though only a small percentage contract postinfectious encephalitis, the number is not inconsiderable. I am firmly convinced that the institution of certain simple measures in management of the child with severe infection can be helpful as prophylaxis. I consider very important (1) bed rest at onset of infection, particularly for the hypertonic child; (2) at least three days of quiet bed rest after the afebrile period in severe infections has been reached, and (3) careful attention to the mental hygiene aspects of the care of the sick child, particularly the avoidance of traumatic experiences as exemplified by the administration of questionable therapy involving violent restraint of the patient.

DR. LOUIS A. LURIE, Cincinnati: There is considerable diversity of opinion regarding the genesis of the psychopathologic train of events seen in postencephalitic types of behavior. According to some, the encephalitis merely brings out character defects and abnormal personality traits that were already present but had been dormant. According to others—and we agree with them—encephalitis does not necessarily accentuate the premorbid personality. As expressed by one investigator, "The tragic feature of encephalitis is personality change, not personality exaggeration." This belief seems to be borne out by the fact that the psychopathologic after-effects of encephalitis are much more pronounced in patients affected early in life. Furthermore, the study reported in this paper shows that the younger the patient affected by the disease, the greater the likelihood of the psychiatric sequelae. The same is true in whooping cough, and I think the reason for that is that the same pathologic changes occur in the brain in cases of encephalitis as they do in whooping cough; namely, petechial hemorrhages. Today the major trend in psychiatry is to explain human behavior in terms of freudian psychology. The tendency to minimize and even to ignore the role of somatic factors in the causation of abnormal behavior has proceeded to the point where even psychiatric social workers feel competent to diagnose and treat behavior disorders of children and adults without the aid of the physician or the psychiatrist. A thorough medical evaluation of the patient is not deemed essential. This attitude on the part of psychiatric social workers has been strengthened by the statements of some psychoanalysts that the usual setup of workers at child guidance clinics, consisting of a psychiatrist, psychologist and psychiatric social worker, can be dispensed with. The claim has been made that any person trained in psychoanalytic concepts and hence psychodynamically oriented is qualified to diagnose and to treat personality disturbances and behavior disorders. Such a trend must not be condoned. As physicians, we must recognize that we cannot separate function from structure. Genetically, function follows structure. The development of the psyche or mind has been coincident and coextensive with the increase in the structural complexity of the cerebral hemispheres; hence, anything that affects the structural integrity of the cortex must necessarily disturb the normal functioning of the psyche or the mind, and hence alter behavior. Encephalitis, as emphasized in this paper, illustrates this point exceptionally well.

PAPAVERINE IN CEREBRAL ANGIOSPASM (VASCULAR ENCEPHALOPATHY)

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Papaverine relaxes many smooth muscles of the body, especially those of the blood vessels. Its therapeutic value has been demonstrated in arterial embolism, in which the drug increases collateral circulation by acting on reflexly constricted vascular channels. Similar therapeutic effect has recently been claimed from its use in angina pectoris and myocardial infarction. Indeed, the experimental and clinical observations of Katz [1] would indicate that papaverine enhances coronary blood flow in these disease states.

The action of papaverine on disturbances of the cerebral circulation has not thus far been reported. Embolism of the cerebral vessels would appear to be an indication for its use. The possible benefit from this drug in the therapy of angiospastic cerebral phenomena commonly observed in the course of hypertensive disease, acute glomerulonephritis, eclampsia gravidarum and lead poisoning has attracted the interest of the writers.

The cerebral manifestations encountered in these conditions vary widely. In the cases of milder disease transient aphasia or hemiplegia may be the only symptom. Headache and vomiting are common. Sensory disturbances consist of numbness, tingling or "crawling" sensations, localized or involving one side of the body, paresthesias of taste and smell as well as sudden temporary loss of vision in one or both eyes. Motor manifestations in the form of clonic convulsive seizures, either localized to one extremity or one side or generalized, are not infrequent. The more severe episodes are generally followed by an interval of clouded consciousness or coma from which the patient recovers in a few hours without recollection of the incident. The transient character of the seizures as well as the rapid clinical recovery following each of them strongly suggests that focal cerebral angiospasm initiates the episodes.

The purpose of this paper, therefore, is to record the results obtained with papaverine hydrochloride in the treatment of encephalopathy associated with hypertensive disease and cerebral vascular disease without hypertension. Although the series studied comprised 46 patients a review of several typical

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1. Elek, S. R., and Katz, L. N.: Some Clinical Uses of Papaverine in Heart Disease, J.A.M.A. 120: 434 (Oct. 10) 1942.

V 13
1948

case records will demonstrate the uniform results obtained.

REPORT OF CASES

CASE 1.—A white Italian woman aged 49 years complained of recurrent attacks of weakness of the left side of the body over a period of three years. Each attack would start with a "creeping" sensation in the left hand and forearm followed by spreading numbness and weakness of the entire left side of the body. Within recent months the patient suffered from five to twenty such attacks daily. The duration of the attack was from several minutes to one hour. Previous treatment with various sedatives failed to control the clinical symptoms. The patient was told that she had epilepsy and was given a trial on diphenylhydantoin sodium without benefit.

Physical examination revealed normal eye grounds. The blood pressure was 112 systolic and 70 diastolic. There was no enlargement of the heart, and no murmurs. There was a normal sinus rhythm with a ventricular rate of 78 per minute. Superficial and deep reflexes were normal. Examination during a typical attack revealed a left hemiparesis and a blood pressure of 120 systolic and 78 diastolic.

The patient was treated with 2 grains (0.12 Gm.) of papaverine hydrochloride and ¼ grain (15 mg.) of phenobarbital orally four times daily. Two mild attacks occurred on the first day of treatment. The patient became symptom free from the second day on. After four weeks of such treatment the dosage was reduced to 1½ grains (0.1 Gm.) of papaverine twice a day. For the ensuing week the patient experienced one or two mild seizures daily. The dosage was increased to the original level, and the patient has remained completely well during the past four months.

CASE 2.—A white Russian woman aged 76 years suffered from recurrent attacks of aphasia and clouded consciousness over a period of twelve years. In recent weeks she had had two to five attacks daily, each lasting from five to fifteen minutes. She had become bedridden during the previous five months because of fear of the seizures and weakness induced by protein deprivation prescribed by her physician. She drank ten to twelve cups of coffee per day.

Physical examination revealed an emaciated elderly white woman. The eye grounds revealed the changes of arteriosclerotic retinopathy. The blood pressure was 190 systolic and 82 diastolic. There was no enlargement of the heart. A soft systolic murmur was heard at the apex. There was a normal sinus rhythm with a rate of 80 per minute. There was no evidence of decompensation. Reflexes were normal.

Treatment consisted of 1½ grains of papaverine hydrochloride with ¼ grain phenobarbital orally three times daily. On this dosage the attacks continued but were diminished in frequency and severity. The patient was placed on a normal diet with coffee excluded. The dosage of papaverine was increased to 3 grains (0.2 Gm.) four times a day. There was complete cessation of attacks. The patient is ambulatory and has led a normal existence for the past year, during which time papaverine has been continued. An attempt to reduce the dosage of the drug on one occasion resulted in recurrence of attacks.

CASE 3.—A white Norwegian woman aged 72 years complained of frequent spells consisting of black circles in front of the eyes and tingling and numbness of the left arm and leg followed by weakness of the entire left side of the body. These symptoms recurred frequently over a period of four months. Each attack lasted several minutes to an hour. Within recent weeks she had had approximately ten attacks daily. Sedatives and hot towels to the head previously employed failed to control these episodes. Patient had had coronary thrombosis three years previously but had enjoyed fair health until the onset of the present symptoms.

Physical examination revealed arteriosclerotic retinopathy with grade 1 hypertensive changes. The blood pressure was 180 systolic and 88 diastolic. There was no enlargement of the heart; no murmurs were heard. There was a normal sinus rhythm and a rate of 84 per minute. There was thickening and tortuosity of the radial vessels. Reflexes were normal.

Treatment consisted of 2 grains of papaverine hydrochloride with ¼ grain phenobarbital three times a day. The recurrence of mild attacks necessitated an increase of papaverine to 4 grains (0.25 Gm.) four times daily, on which dosage the patient became symptom free. After a period of four months the dosage of papaverine was reduced to 4½ grains (0.28 Gm.) daily, and the patient has continued to remain asymptomatic for the past two months.

CASE 4.—A white Italian man aged 38 years with advanced malignant hypertension suffered from recurrent blindness and acute mania. His attacks recurred three to four times weekly, lasting one hour and followed by a period of coma from which he recovered without recollection of the incident. Enormous doses of sedatives failed to control or prevent these seizures.

Physical examination revealed grade 4 hypertensive retinopathy. The heart was moderately enlarged to the left. There was a systolic murmur at the apex. The aortic second sound was markedly accentuated. There was a normal sinus rhythm with a ventricular rate of 80 per minute. The blood pressure was 286 systolic and 160 diastolic. Reflexes were essentially normal.

The patient was given 3 grains of papaverine hydrochloride and ½ grain (30 mg.) phenobarbital orally four times daily. The patient worked for two weeks at his usual occupation without a single seizure. Attacks recurred after this period and necessitated hospitalization. Sympathectomy was performed without material reduction in the blood pressure. Cerebral episodes continued to recur during the postoperative period. The patient was then placed on 15 grains (1 Gm.) of papaverine daily and has suffered no attacks for a period of two months.

COMMENT

Our studies indicate that papaverine hydrochloride is of considerable value in the prevention of attacks of vascular encephalopathy. In most instances continuous administration of the drug resulted in complete cessation of symptoms. Papaverine abolished frequently recurring cerebral episodes in 2 patients who had suffered from this syndrome for a number of years. The drug was found effective in decreasing the severity and frequency of seizures even in some patients with advanced malignant hypertension.

Dosage varies considerably with each case. In some instances a daily dosage of 4½ grains was adequate to prevent the attacks. In others, symptoms continued to recur until 12 to 18 grains (0.75 to 1.2 Gm.) per day was administered. In a few cases the dosage has been considerably reduced without recurrence of symptoms. One case has required 9 grains (0.6 Gm.) daily for over a year to maintain freedom from attacks.

The toxicity of papaverine is low, so that the ingestion of ten times its therapeutic dose would not result in untoward effects.[2] It is devoid of narcotic action and causes neither sleep nor analgesia.

Although barbiturates failed to control the cerebral episodes in our cases, the combination of phenobarbital (grains ¼ to ½) with papaverine appeared to reduce the dosage of the latter required for clinical improvement. Conversely, the use of coffee or tea in excess seemed to vitiate the effectiveness of papaverine.

The cases studied do not substantiate the view that this cerebral syndrome is correlated with arterial hypertension.[3] Indeed, observation of several patients with cerebral vascular disease without

2. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, the Macmillan Company, 1941.
3. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1939.

hypertension disclosed normal blood pressure levels during typical seizures. Furthermore, in none of these cases was cardiac insufficiency a possible factor in the pathogenesis of the syndrome. It would appear, therefore, that vascular encephalopathy is a more appropriate designation than hypertensive encephalopathy for this cerebral symptom-complex.

The favorable response in our cases to papaverine suggests the possibility of comparable benefit from this drug in the encephalopathic episodes of acute glomerulonephritis, eclampsia gravidarum and lead poisoning. Similar response in these conditions would add further indirect evidence that the cerebral syndrome is initiated by angiospastic phenomena.

SUMMARY AND CONCLUSIONS

Papaverine hydrochloride was administered orally to 46 patients suffering from cerebral episodes associated with hypertensive disease or cerebral vascular disease without hypertension. The drug was found to be highly effective in preventing the recurrence of seizures. The amount of papaverine necessary for optimum results was frequently three to four times the commonly accepted therapeutic dosage. In some instances 12 to 18 grains per day was required for the control of symptoms. The favorable response in our cases to papaverine is further indirect evidence that the cerebral episodes are initiated by angiospastic phenomena. Vascular encephalopathy may occur in the absence of arterial hypertension. Several illustrative cases have been reported. Trial of this drug in the encephalopathic seizures of acute glomerulonephritis, eclampsia gravidarum and lead poisoning is indicated.

ADDENDUM

Since this paper was submitted for publication 3 cases of vascular encephalopathy associated with acute glomerulonephritis were controlled successfully by large oral doses of papaverine. In addition, 2 cases of retinal angiospasm complicating hypertensive disease responded rapidly to the intravenous administration of this drug. Papaverine in adequate oral dosage was similarly effective in the treatment of a large number of cases of "hypertensive headache."

Infectious Diseases.—Of the many triumphs over human disease for which modern medicine deserves credit, perhaps none is more notable than the power to control the activity of the micro-organisms that cause infectious disease. From the time of the discovery by Pasteur of the essential relationship of bacteria to certain diseases of mankind, progress in the direction of prevention and cure has been rapid and continuous. In fact, many of the destructive plagues that in past ages brought death and disability to vast populations of the world have now entirely disappeared or become inconsequential wherever modern medical technics are understood and efficiently applied. Furthermore, such infectious diseases as are still prevalent are yielding in an almost miraculous manner to the more recent advances of medical science. Medicine finds its most appropriate field of successful activity in the stabilized populations and efficiently organized communities that progressively evolve during period of peaceful and harmonious human relations. In wartime, on the other hand, the varying disruptive influences of military conflict disturb the favorable effects of this equilibrium.—Dochez, A. R.; MacLeod, C. M., and McCormack, J. E.: Advances in Military Medicine, vol. I, Boston, Little, Brown and Company, 1948.

Clinical Notes, Suggestions and New Instruments

MASSIVE USE OF OXIDIZED GAUZE IN HEMORRHAGE FROM A MAJOR VESSEL

GEORGE A. STEWART, M. D.
and
JAMES N. CIANOS, M. D.
Baltimore

Since the preparation of oxidized gauze by Kenyon,[1] there has been an increasing use of this hemostatic agent wherever bleeding cannot be controlled by the ordinary methods of ligature or suture. Experimental work[2] in which small amounts of the material were buried in parenchymatous and supporting tissues of animals showed the gauze to be completely absorbable. There was, moreover, but slight reaction to the gauze, since there could be seen only minimal proliferation of glial and connective tissue. In no case were adhesions produced. However, when the gauze was placed in serous cavities such as the peritoneum, cysts were sometimes formed which were eventually resorbed.[3] Putnum[4] employed oxidized gauze impregnated with thrombin in thirty neurosurgical operations and reported gratifying results.

According to Frantz and associates,[5] oxidized gauze has an affinity for hemoglobin. As soon as it is soaked by blood, it turns into a brown or black mass, swells and becomes sticky. This adhering mass then effects hemostasis by taking the place of the clot that would form in the normal course of events. Reparative tissue does not invade the mass thus formed, which has a tendency to become rather friable within twenty-four hours. Healing takes place normally and the mass does not seem to be incorporated in the ensuing scar. Phagocytes which show large basophilic droplets within their cytoplasm later surround the gauze. This reaction seems to be pathognomic for oxidized gauze.

In a review of the literature, no instance could be found in which oxidized gauze was used in large quantities or in which it was used solely as a means of arresting bleeding from a major vessel. Frantz warned[3] that gauze should be used in as small a quantity as possible and also where wounds can be closed without drainage. In some instances[6] a small amount of gauze has been used in conjunction with ordinary packing and the latter was removed in twenty-four hours. In every case, however, the bleeding seems to have been a generalized ooze from raw surfaces rather than active hemorrhage from an artery or vein.

REPORT OF CASE

The patient, a white woman aged 53, was admitted to the hospital on June 22, 1947 with a diagnosis of thrombophlebitis of the left lower extremity. The present illness began suddenly on June 6, with pain in the left sural region. The pain continued to increase in severity and ascend along the leg to the groin. On the day of admission the pain was also felt in the left lower part of the abdomen and it was associated with nausea and vomiting. At about this time the leg began to swell. The remaining history was essentially negative except for a cesarean section which the patient had in 1935. This was unattended by any complications.

Physical examination showed a well nourished white woman complaining of pain in the left lower extremity. There was tenderness to deep palpation over the left lower quadrant of the abdomen. Tenderness in this region was also elicited by bimanual pelvic examination. The left lower extremity was

1. Yackel, E. C., and Kenyon, W. O.: J. Am. Chem. Soc. **64**: 121, 1942. Unruh, C. C., and Kenyon, W. O.: ibid. **64**: 127, 1942.
2. Frantz, V. K.: Ann. Surg. **118**: 116, 1943.
3. Frantz, V. K.; Clarke, H. T., and Lattes, R.: Ann. Surg. **120**: 181, 1944.
4. Putnum, T. J.: Ann. Surg. **118**: 127, 1943.
5. Studdiford, W. E.: Am. J. Obst. & Gynec. **52**: 495, 1946.

V 13
1948

moderately edematous and of a pale cyanotic discoloration. It was cooler than the opposite extremity and exquisite tenderness was present in the region of the calf, along the course of the saphenous vein and over the femoral triangle.

The patient was placed on anticoagulants, lumbar sympathetic blocks and rest. The prothombin time was maintained at twenty-nine seconds. However, she failed to respond to this treatment, and the pain and swelling of the extremity seemed to increase. It was, consequently, decided to explore the deep veins.

With the patient under spinal "pentathol sodium" analgesia, the retroperitoneal space in the left side was exposed through a muscle-splitting incision. The peritoneum was peeled away from the posterior abdominal wall. The ureter was identified and retracted medially. The common iliac artery, which was adherent to the veins by periphlebitis, was carefully separated and retracted laterally. It was observed that the clot had ascended to the distal third of the common iliac vein, which was exposed preparatory to ligature. During this procedure a Deaver retractor which was used to retract the medial lip of the wound lacerated the common iliac vein. Immediately the field was flooded with blood. This was temporarily stopped by digital pressure and then packing. However, as soon as the pressure was removed, the vein bled just as before. Attempts to clamp the vessel merely caused it to tear proximally toward the inferior vena cava. The patient's condition was too precarious to expose and ligate the inferior vena cava through a midline incision. She was given 2,000 cc. of citrated blood and 1,000 cc. of plasma. It was decided as a last resort to pack the retroperitoneal space with oxidized gauze.[6] The contents of sixteen ampules were placed snugly against the bleeding area and held in position by a gauze pack for ten minutes. The patient's condition improved and, on removal of the pressure, it was found that there was no additional hemorrhage. The wound was quickly closed without drainage. The patient made an uneventful recovery and the wound healed per primum. Swelling and pain of the leg gradually subsided. Examination six weeks after the operation showed the wound to be well healed. There was no evidence of any mass or tenderness. The pain and swelling of the leg were completely absent and the patient stated that she experienced no difficulty.

SUMMARY

A case is reported in which massive use of oxidized gauze was used to arrest hemorrhage from a major vessel. No ill effects were observed and the gauze was apparently completely absorbed. In this particular instance enough gauze was used to act both chemically and by pressure in order to arrest bleeding.

6. Prepared by Parke, Davis & Company.

Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

AUSTIN SMITH, M.D., *Secretary*

AMINOPHYLLINE (See New and Nonofficial Remedies, 1947, p. 305).

The following dosage forms have been accepted:
GEORGE A. BREON & Co., KANSAS CITY, MO.

Tablets Aminophylline: 100 mg. and 200 mg.

Solution Aminophylline with Benzyl Alcohol 2%: 0.48 Gm. in 2 cc. ampuls.

Solution Aminophylline: Ampuls 0.25 Gm. in 10 cc. and 0.5 Gm. in 20 cc.

LINCOLN LABORATORIES, INC., DECATUR, ILL.

Solution Aminophylline: 0.48 Gm. in 2 cc. and 20 cc. ampuls and 0.24 Gm. in 10 cc. ampuls.

AMINO ACID PREPARATIONS (See New and Nonofficial Remedies, 1947, p. 382).

The following dosage form has been accepted:
MEAD JOHNSON & COMPANY, EVANSVILLE, IND.

Protolysate (*Powder*): 454 Gm. containers. A casein hydrolysate prepared by digestion with fish caceca for oral administration.

DIETHYLSTILBESTROL (See New and Nonofficial Remedies, 1947, p. 347).

The following dosage forms have been accepted:
COLE CHEMICAL CO., ST. LOUIS, MO.

Tablets Diethylstilbestrol: 1 mg.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls containing 1 mg. per cc. in peanut oil.

PHENOBARBITAL SODIUM (See New and Nonofficial Remedies, 1947, p. 418).

The following dosage form has been accepted:
THE WARREN-TEED PRODUCTS CO., COLUMBUS, OHIO

Solution Phenobarbital Sodium with Benzyl Alcohol 2% in Propylene Glycol: 0.13 Gm. per cc., 1 cc. ampuls.

ESTROGENIC SUBSTANCES (WATER INSOLUBLE) (See New and Nonofficial Remedies, 1947, p. 343).

The following dosage forms have been accepted:
CARROLL DUNHAM SMITH PHARMACAL CO., NEW BRUNSWICK, N. J.

Solution Estrusol in Oil with Benzyl Alcohol 3%: 20,000 international units per cubic centimeter in 1 cc. ampuls and 5 cc. and 15 cc. vials in peanut oil.

Solution Estrusol in Oil: 2,000, 5,000 or 10,000 international units per cubic centimeter in 1 cc. ampuls and 2,000 or 10,000 international units per cubic centimeter in 15 cc. vials in peanut oil. Preserved with 0.5 per cent chlorobutanol.

Aqueous Suspension Estrusol: 20,000 international units per cubic centimeter in 1 cc. ampuls, 5 cc. and 15 cc. vials. 1 cc. contains the equivalent of 20,000 international units of estrogenic substances, water insoluble in isotonic sodium chloride solution. Vials preserved with 0.5 per cent chlorobutanol.

THIAMINE HYDROCHLORIDE (See New and Nonofficial Remedies, 1947, p. 506).

The following dosage form has been accepted:
REED & CARNRICK, JERSEY CITY, N. J.

Solution Thiamine Hydrochloride: 50 mg. per cc. in 10 cc. vials. Preserved with 0.5 per cent chlorobutanol.

PENICILLIN (See New and Nonofficial Remedies, 1947, p. 144).

The following additional dosage forms have been accepted:
PREMO PHARMACEUTICAL COMPANY, INC., NEW YORK

Nebutabs Crystalline Penicillin G Sodium: 50,000 units of crystalline penicillin G sodium, tableted without diluent for use in the preparation of solutions for nebulization. Packaged in boxes containing 24 Nebutabs and also in packages of 12 Nebutabs with an oral nebulizer or with a nasal nebulizer.
U. S. patent applied for.

Crystalline Penicillin G Potassium in Oil and Wax: 300,000 units per cubic centimeter, 5 cc. and 10 cc. vials. Penicillin G potassium suspended in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P.

STREPTOMYCIN (See New and Nonofficial Remedies, 1947, p. 150).

The following dosage form has been accepted:
E. R. SQUIBB & SONS, NEW YORK

Streptomycin Hydrochloride: 20 cc. vials containing streptomycin hydrochloride equivalent in activity to 1 Gm. of streptomycin base and 40 cc. vials containing streptomycin hydrochloride equivalent in activity to 2 Gm. of streptomycin base.

136
948

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SATURDAY, APRIL 3, 1948

EDITORIAL ANNOUNCEMENT

The absence of the compositors employed by the American Medical Association from their work continues. This issue of THE JOURNAL has been prepared largely by the use of Vari-Typer machines. Because of the difficulties of reorganization of the headquarters office necessitated by this situation, the editorial material in this issue of THE JOURNAL has been greatly condensed.

HEPATIC CIRRHOSIS TREATED WITH METHIONINE

In January 1947 the Council on Pharmacy and Chemistry reported on the status of methionine in the prevention and treatment of injury to the liver.[1] Certain chemical agents produced lesions in the liver of experimental animals closely resembling those seen in man in portal cirrhosis. Much experimental evidence is available indicating that injury of the liver may be produced by dietary deficiencies. Gyorgy and Goldblatt[2] found that necrosis or cirrhosis of the liver would develop in rats on a low protein diet and that the administration of choline would prevent the development of these conditions. Daft, Sebrell and Lillie[3] confirmed this work and found also that some protection to the liver was afforded by the addition of choline, methionine and casein. In a later report[4] Gyorgy and Goldblatt concluded that the cirrhosis produced in animals by a low protein diet could be prevented by a combination of choline and cystine or by methionine alone. The Council in its report emphasized, however, that the experimental dietary cirrhosis seen in animals is not histologically the same as portal cirrhosis in man and that the experiments need clinical confirmation on human patients.

Since the Council's report was published a study on a group of patients with cirrhosis has been reported[5] by Beams and Endicott. Nine patients with cirrhosis in the decompensated stage were given dl-methionine by mouth; 3 patients who were extremely ill first received a 2 per cent solution of the agent by vein from eight to twenty days preceding the oral administration. All patients in this group were given a high protein, low fat diet and 45 Gm. of brewers' yeast a day, except 1 patient who was not able to take so much protein and yeast. All except 1 patient received also 5 cc. of crude liver extract three times a week. A second group of 5 patients, including 2 who had been treated with methionine supplement and had had recurrences, received the same treatment as the first group except for methionine supplement. The food intake of most of both groups was calculated daily. The diet provided from 2 to 5 Gm. of methionine a day. Liver needle biopsies were obtained before treatment started and again after periods of several weeks of treatment. Other laboratory studies were done at frequent intervals.

The 9 patients who received methionine supplement showed histologic changes in the liver which indicated a favorable response to the treatment; 5 patients in this group, 1 of whom did not receive crude liver extract, showed clinical improvement also, and 3 of them have remained well for from one to two years. Two of the 5 patients ate poorly, continued to drink intoxicating liquor after discharge from the hospital and had recurrences, 1 after twelve months and 1 after seven months.

While the histologic changes in the liver indicating favorable response to treatment occurred in both groups of patients, a definite difference was observed in the number of patients who showed such changes and in the degree of change. In those who received methionine supplement the changes were striking. The parenchymal cells revealed definite improvement in histologic appearance, and there was a disappearance of fat. The only difference in the treatment of the two groups was the use of methionine supplement. The author concludes, therefore, that methionine was responsible for the different results obtained.

1. The Status of Methionine in the Prevention and Treatment of Liver Injury, report of the Council on Pharmacy and Chemistry, J.A.M.A. 133:107 (Jan. 11) 1947.
2. Gyorgy, P., and Goldblatt, H.: Proc. Soc. Exper. Biol. & Med. 46:492-494, 1941.
3. Daft, F.S.; Sebrell, W.H., and Lillie, R.D.: Proc. Soc. Exper. Biol. & Med. 48:228-229, 1941.
4. Gyorgy, P., and Goldblatt, H.: J. Exper. Med. 75:191-195, 1942.
5. Beams, A.J., and Endicott, E.T.: Gastroenterology 9:718-735, 1947

V 13 1948

In one half of the cases the improved histologic picture was accompanied by improvement in the clinical course and, in some, of the liver function tests also. An increase in sulfobromophthalein sodium excretion was a fairly constant observation. In the other half of the cases no correlation was noted between the histologic changes and the clinical course or hepatic function. Two patients improved clinically but did not show histologic changes, and 1 of them did not show improved function of the liver. An adequate explanation is not available for the correlation between the histologic changes, laboratory results and clinical course in some patients and not in others. Possible in those who showed an improved histologic picture without improvement in the clinical or laboratory observations the perilobular fibrosis isolated hepatic lobules or groups of cells in a manner that interfered with the portal circulation and obstructed the biliary capillaries.

Thus all the patients who received the methionine supplement showed histologic changes indicating a favorable response irrespective of a high protein diet, crude liver extract or brewers' yeast. Among the patients who did not receive methionine supplement only 1 showed significant histologic changes after treatment. Clinical improvement and improvement in hepatic function were associated with histologic changes in 7 patients, 6 of whom received methionine supplement and 1 of whom did not.

This study suggests that methionine was responsible for the improved histologic changes in the liver which occurred in these patients.

Current Comment

THE WORLD HEALTH ORGANIZATION

Recently the Rules Committee of the House of Representatives tabled a bill to ratify the constitution of the World Health Organization and make the United States a member of that body. Already twenty-three other nations have signed the constitution of W.H.O., and the three additional ratifications necessary to complete organization will unquestionably become effective within the next few weeks. The first meeting of the new World Health Organization has been called in Geneva, Switzerland, in June 1948. This means, no doubt, that the United States will not be present as a member. Unfortunately a statement has not appeared as to why the Rules Committee took the action mentioned. Unless there are reasons which are secret and not available, the failure of the Rules Committee to recommend positive action is an embarrassment to American leaders in the field of health. The American Medical Association has thus far participated in the development of the World Health Organization and has also played a leading role in the organization of the World Medical Association. There has seemed to be every reason why these two bodies could cooperate for the advancement of world health. Some of the projects which the Interim Commission of the World Health Organization has been studying include international agreements for the control of quarantine and isolation and for the prevention and spread of infectious diseases; the establishment of international standards for biologic and similar agents, and the development and circulation of scientifically collected vital statistics. The Rules Committee which has rejected participation by the United States in this activity would do well to explain the action taken to the American agencies interested in public health which have thus far strongly supported participation by our government in the World Health Organization.

PRESCRIBING OF PHARMACEUTIC SPECIALTIES

At a recent meeting, the Council on Pharmacy and Chemistry considered complaints from physicians who wished to incorporate some of the newer drugs in their prescriptions. These could not be filled readily because of the unavailability of the product in bulk forms. These physicians requested the Council to require manufacturers to supply their drugs in bulk form before consideration would be given to the product for inclusion in New and Nonofficial remedies. The Council did not consider it feasible to make such a requirement but expressed the opinion that pharmaceutic manufacturers should be informed of the desirability of making drugs available in powdered or bulk form. The growing tendency to make all drugs available in ready-made dosage forms has been the result of a number of factors. Economy, accuracy in dosage and pharmaceutic elegance are among the immediate reasons. The development of new potent or specific remedies and the decline of polypharmacy are among the more basic reasons for this trend. The result of this trend has tended to diminish the individualization of therapy. The treatment of disease is only one aspect of the treatment of the patient. The therapy prescribed should be designed to fit the needs of the individual patient and not the "average" patient. Rational combinations of drugs are required on occasion as well as dosages not available from the stocks of a commercial supplier. If the drugs are not available in bulk form, the pharmacist either cannot fill the prescription or must laboriously convert one dosage form into another.

ORGANIZATION SECTION

Washington Letter

(From a Special Correspondent)

April 2 1948.

Congress Studies Military Training and Draft Legislation

Congress has under consideration the recommendations of President Truman for expanded defense forces, and enactment of universal military training and the draft. The armed services have submitted to the President alternate defense plans calling for from $2,000,000 to $11,000,000 more than the proposed $11,000,000,000 military budget for fiscal 1949. Testifying before the Senate Armed Services Committee, Dr. Karl T. Compton, president of Massachusetts Institute of Technology, declared that some educational groups and educators were hasty and ill-informed in opposing a training program. On the question of reestablishing the draft, the American Veterans of World War II have recommended that disabled veterans of 1941-45 be given key posts on selective service boards. Republican senators have indicated that they might consent to register, but delay the drafting of, young men for military service.

Only Twenty-Eight Doctors Accused of Overcharging Veterans

Although there are in the United States about 85,000 physicians authorized to give veterans hometown treatment on the basis of billing the Veterans Administration for the expense under a set schedule of fees, only twenty-eight physicians have been accused by the agency of irregularities. Their names have been given to the American Medical Association, the agency reported. Alleged offenses range from minor violations of regulations to fraud. One physician is accused of charging the agency $160 for treatment of a veteran and of billing the same treatment for another $100. Names of the physicians were not disclosed. Of twenty removed from the authorized lists, five were in the New York region, four in Philadelphia, four in Pittsburgh, three in Chicago, and one each in Norfolk, Va.; Minneapolis, Wichita, Kan., and San Francisco.

Criticism of Condon Described as Threat to Research

Dr. David R. Inglis, Johns Hopkins University physicist and a former member of the Los Alamos atomic energy laboratory, told a meeting of the Washington Association of Scientists that the action of a House Committee in questioning the loyalty of Dr. Edward U. Condon, director of the National Bureau of Standards, was a threat to scientists and scientific research. He said: "There are large implications to these attacks; first, those pertaining to science and scientists—the contributions of scientists to the national welfare—and, second, those pertaining to the constitutional liberties of all citizens." With reference to the vast program of governmental research, he said that such technics of character assassination mean that scientists and engineers will "be very reluctant to enter federal research agencies." He added that 'the witch hunt might even be extended to embrace all scientists as a class."

St. Elizabeths Hospital

Dr. Winfred Overholser, superintendent of St. Elizabeths Hospital, stated in his annual report, forwarded to Congress by Federal Security Administrator Oscar R. Ewing, that dangerous mental patients are kept in an inadequate building which should be replaced by a new four hundred bed security unit. He said that limited space made it necessary to keep dangerously aroused patients and those under criminal charges in a building which was built more than thirty years ago.

George Washington University Hospital Opened to Public

The public and press of the capital accorded a cordial "welcome" to newly opened four hundred bed George Washington Univerait Hospital. The $4,000,000 structure is the first of several buildings that the university plans to have in its medical center. The modern character of the hospital impressed visitors.

State Legislation

Kentucky

Bill Introduced.—H. 424, relating to hospitals, proposes that no hospital shall deny admission to the patient of any licensed physician at any time that there are in the hospital beds and room facilities suitable for such patient and further proposes that no hospital shall enter into any agreement with any physician or group of physicians pursuant to which any bed or room facilities in the hospital are to be reserved for unnamed patients of such physicians or pursuant to which such physicians are allocated or assigned certain bed or room facilities for their patients.

Bills Passed.—H. 447 passed the senate March 19. It authorizes any hospital or other institution offering accredited courses of instruction in nursing, medicine, surgery, or other related courses of graduate study or on the professional level, to elect by a majority vote of its governing body to receive as pupils persons of all races. S. 105 passed the house March 10. It proposes the creation of a medical research commission to provide for a program of research in the fields of medicine, surgery and allied sciences, preventive medicine, control of diseases and all other features of medicine and surgery that affect the health and welfare of the people of the state. S. 197 passed the house March 18. It proposes the creation and establishment of a division of medical hospitals and related services in the department of health to make a survey of hospital facilities throughout the state and to accept federal funds to assist in the construction of additional needed facilities. The proposal would also require the appointment of an advisory council and the preparation of necessary regulations and standards pertaining to the conduct and operation of hospitals which are constructed by virtue of the act. S. 342 passed the house March 19. It proposes to create a Kentucky Building Commission to have charge of buildings constructed throughout the state and proposes that appropriations to this commission shall be used, among other things, for matching funds for hospital construction under any law now existing or that may be passed by the national Congress.

Mississippi

Bills Introduced.—H. 687 proposes the enactment of a hospital licensing law and, in conjunction therewith, the appointment of an advisory hospital council to consult and advise with the licensing agency and to assist in the development of rules, regulations and standards to be required of hospitals seeking licensure. H. 717 proposes an appropriation to defray the expenses of the state program of eradication and control of syphilis and other venereal diseases. H. 818 proposes an appropriation to the Mississippi commission on hospital care for the purpose of building, erecting and equipping hospitals and other facilities within the state of Mississippi. S. 453 proposes an enabling act for the organization and operation of nonprofit hospital, medical and surgical service corporations.

V 13
1948

Coming Medical Meetings

Alabama, Medical Association of the State of, Mobile, April 15-17. Dr. D. L. Cannon, 519 Dexter Ave., Montgomery 4, Secretary.

American Association for the Study of Goiter, Toronto, Can., King Edward Hotel, May 6-8. Dr. Thomas C. Davison, 478 Peachtree St.N.E., Atlanta, Ga., Secretary.

American Association of Anatomists, Madison, Wis., April 21-23. Dr. Normand L. Hoerr, 2109 Adelbert Road, Cleveland 6, Secretary.

American Association of Genito-Urinary Surgeons, Skytop, Pa., Skytop Lodge, May 12-14. Dr. Norris J. Heckel, 122 S. Michigan Ave., Chicago 3, Secretary.

American Association of Plastic Surgeons, Boston, May 6-8. Dr. W. H. Steffensen, 1810 Wealthy St.S.E., Grand Rapids, Mich., Secretary.

American Association of the History of Medicine, Philadelphia, Penn Sheraton Hotel, May 26-27. Dr. Howard Dittrick, 2020 E. 93d St., Cleveland 6, Secretary.

American Association on Mental Deficiency, Boston, Hotel Statler, May 12-15. Dr. Neil A. Dayton, Box 51, Mansfield Depot, Conn., Secretary.

American Broncho-Esophagological Association, Atlantic City, Chalfonte-Haddon Hall, April 7-8. Dr. Paul H. Holinger, 700 N. Michigan Ave., Chicago 11, Secretary.

American College of Physicians, San Francisco Civic Auditorium, April 19-23, Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Secretary.

American Dermatological Association, Coronado, Calif., April 26-29. Dr. Harry R. Foerster, 208 E. Wisconsin Ave., Milwaukee, Secretary.

American Federation for Clinical Research, Atlantic City May 4. Dr. John S. LaDue, 139 E. 36th St., New York 16, Secretary.

American Gastro-Enterological Association, Atlantic City, Claridge Hotel, April 30-May 1. Dr. Dwight L. Wilbur, 655 Sutter St., San Francisco, Secretary.

American Hearing Society, Pittsburgh, May 19-23. Mrs. Frances E. Lee, 817 Fourteenth St. N.W., Washington 5, D. C., Secretary.

American Laryngological Association, Hot Springs, Va., April 14-15. Dr. Louis H. Clerf, 1530 Locust St., Philadelphia 2, Secretary.

American Laryngological, Rhinological and Otological Society, Atlantic City, April 7-9. Dr. C. Stewart Nash. 277 Alexander St., Rochester, N. Y., Secretary.

American Ophthalmological Society, Hot Springs, Va., May 16-19. Dr. Walter S. Atkinson, 129 Clinton St., Watertown, N. Y., Secretary.

American Orthopsychiatric Association, New York, Hotel Commodore, April 12-14. Nina Ridenour, Ph.D., 1790 Broadway, Rm. 916, New York 19, Secretary.

American Otological Society, Hot Springs, Va., April 12-13. Dr. Gordon D. Hoople, 713 E. Genesee St., Syracuse 2,N. Y., Secretary.

American Pediatric Society, Quebec, Can., May 24-26. Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12, Secretary.

American Physiotherapy Association, Chicago, La Salle Hotel, May 23-28. Miss Mildred Elson, 1790 Broadway, New York 19, Executive Secretary.

American Psychiatric Association, Washington, D. C., Statler Hotel, May 17-20. Dr. Leo H. Bartemeier, General Motors Bldg., Detroit 2, Secretary.

American Society for Clinical Investigation, Atlantic City, Haddon Hall, May 3. Dr. Eugene A. Stead Jr., Duke Hospital, Durham, N. C., Secretary.

American Society for Research in Psychosomatic Problems, Atlantic City, May 1-2. Dr. Eugene Ferris, 714 Madison Ave., New York 21. Secretary.

American Student Health Association, Detroit, Hotel Statler, May 7-8. Dr. George T. Blydenburgh, Ohio Wesleyan University, Delaware, Ohio, Secretary.

American Urological Association, Boston, Hotel Statler, May 17-20. Dr. Thomas D. Moore, 899 Madison Ave., Memphis 3, Tenn., Secretary.

Arizona State Medical Association, Phoenix, Hotel Westward Ho, May 19-21. Dr. Frank J. Milloy, 234 N. Central Ave., Phoenix, Secretary.

Arkansas Medical Society, Little Rock, Robinson Auditorium, April 15-17. Dr. W. R. Brooksher, 602 Garrison Ave., Fort Smith, Secretary.

Association of American Physicians, Atlantic City, May 4-5. Dr. Henry M. Thomas Jr., 1201 N. Calvert St., Baltimore 2, Secretary.

California Medical Association, San Francisco, April 11-14. Dr. L. Henry Garland, 450 Sutter St., San Francisco 8, Secretary.

Connecticut State Medical Society, Fairfield, April 27-29. Dr. Creighton Barker, 258 Church Street, New Haven, Secretary.

Florida Medical Association, St. Augustine, Ponce de Leon Hotel, April 11-14. Dr. Robert B. McIver, 111 W. Adams St., Jacksonville, Secretary.

Georgia, Medical Association of, Atlanta, April 27-30. Dr. Edgar D. Shanks, 478 Peachtree St. N.E., Atlanta Secretary.

Hawaii Territorial Medical Association, Honolulu, May 6-9. Dr. Harry L. Arnold Jr., 510 S. Beretania St., Honolulu 53, Secretary.

Illinois State Medical Society, Chicago, Palmer House, May 10-12. Dr. Harold M. Camp, 224 S. Main St., Monmouth, Secretary.

International Congresses on Tropical Medicine and Malaria, Washington, D.C., May 10-18. Dr. Wilbur A. Sawyer, Department of State, Washington 25, D.C., Executive Secretary.

Iowa State Medical Society, Des Moines, April 18-21. Dr. John C. Parsons, 406 Sixth Ave., Des Moines 9, Secretary.

Kansas Medical Society, Wichita, The Forum, May 10-13. Dr. Dale D. Vermillion, 512 New England Bldg., Topeka, Secretary.

Louisiana State Medical Society, Monroe, April 12-14. Dr. P. T. Talbot, 1430 Tulane Ave., New Orleans 13, Secretary.

Maryland, Medical and Chirurgical Faculty of the State of, Baltimore, April 27-28. Dr. George H. Yeager, 1211 Cathedral St., Baltimore, Secretary.

Massachusetts Medical Society, Boston, Hotel Statler, May 25-27. Dr. H. Quimby Gallupe, 8 Fenway, Boston 15, Secretary.

Mississippi State Medical Association, Jackson, May 11-13. Dr. T. M. Dye, Box 295, Clarksdale, Secretary.

National Society for the Prevention of Blindness, Minneapolis, Hotel Radisson, April 5-7. Mrs. Eleanor Brown Merrill, 1790 Broadway, New York 19, Executive Director.

Nebraska State Medical Adsociation, Lincoln, Hotel Cornhusker, May 3-6. Dr. R. B. Adams, 416 Federal Securities Bldg., Lincoln 8, Secretary.

New England Dermatological Society, Boston, April 14. Dr. G. Marshall Crawford, 1180 Beacon St., Brookline, Secretary.

New Jersey, Medical Society of Atlantic City, Haddon Hall, April 26-29. Dr. Earl LeRoy Wood, 315 W. State St., Trenton, Secretary.

North Carolina, Medical Society of the State of. Pinehurst, May 3-5. Dr. Roscoe D. McMillan, P.O. Box 232, Red Springs, Secretary.

North Dakota State Medical Association, Jamestown, May 23-28. Dr. O. A. Sedlak, 792 First Ave. S., Fargo, Secretary.

Northern Tri-State Medical Association, Findlay, Ohio April 14. Dr. F. Cameron, 247 W. Berry St., Fort Wayne, Indiana, Secretary.

Ohio State Medical Association, Cincinnati, Netherland Plaza Hotel, March 30-April 1. Mr. C. S. Nelson, 79 E. State St., Columbus 15, Secretary.

Oklahoma State Medical Association, Oklahoma City, Skirvin Hotel, May 17-19. Mr. R. H. Graham, 210 Plaza Court, Oklahoma City, Executive Secretary.

Post Graduate Institute of the Philadelphia County Medical Society, Philadelphia, Bellevue-Stratford Hotel, April 20-23. Dr. Gilson Colby Engel, 301 S. 21st St., Philadelphia, Director.

Rhode Island Medical Society, Providence, May 12-13. Dr. Morgan Cutts, 106 Francis St., Providence 3, Secretary.

Society of American Bacteriologists, Minneapolis, Nicollet Hotel, May 10-14. Dr. Leland W. Parr, 1335 H St. N. W., Washington 5, D. C., Secretary.

Society of Biological Psychiatry, Washington, D.C., May 16. Dr. George N. Thompson, 1136 W. Sixth St., Los Angeles 14, Secretary.

South Carolina Medical Association, Charleston, Francis Marion Hotel, May 12-14. Dr. Julian P. Price, 105 W. Cheves St., Florence, Secretary.

Southeastern Surgical Congress, Hollywood, Fla., Hollywood Beach Hotel, April 5-8. Dr. Benjamin T. Beasley, 45 Edgewood Avenue S.E., Atlanta 3, Ga., Secretary.

Southern Society of Clinical Surgeons, Chicago, May 26-28. Dr. William P. Nicolson Jr., 478 Peachtree St. N.E., Atlanta, Ga., Secretary.

Southwest Allergy Forum, Oklahoma City, April 5-6. Dr. Fannie Lou Leney, 1200 N. Walker St., Oklahoma City, Secretary.

Tennessee State Medical Association, Nashville, April 13-14. Dr. W. M. Hardy, 706 Church St. Nashville 3, Secretary.

Texas, State Medical Association of, Houston, Rice Hotel, April 26-29. Dr. Harold M. Williams, 1404 W. El Paso St., Fort Worth, Secretary.

Western Association of Industrial Physicians and Surgeons, San Francisco, Fairmont Hotel, April 10. Dr. Christopher Legge, Crockett, Calif. Secretary.

Western Section American Urological Association, Victoria, B. C., Empress Hotel, April 19-21. Dr. Adolph A. Kutzmann, 1930 Wilshire Blvd., Los Angeles, Secretary.

GOVERNMENT SERVICES

ARMY

MODIFICATION OF THE MUNSON SHOE LAST

The Army's service and combat footwear has been made over the Munson last since 1912. Brig. Gen. Edward L. Munson, of the Army Medical Corps, then a lieutenant colonel, designed the last after the most comprehensive study of the human foot in relation to military footwear ever undertaken by the Army up to that time. The Munson last served American soldiers in two great wars and at the time of its development was the most scientific approach ever made to properly fitting the soldier's foot. However, World War II demonstrated that the shoes and boots fitted too closely over the little toe area and wore out too quickly because of the excessive roundness of the bottom forepart of the last. To overcome these deficiencies, the last has now been modified to allow 1/8 inch (0.3 cm.) more room in the forepart of the shoe and to reduce the roundness of the bottom forepart across the tread.

Modification of the Munson last is only an interim step in a long range project which contemplates a completely new last. Two major surveys have determined the actual shapes and measurements of men's feet representing the Army as a whole. One, conducted by the Army Medical Research Laboratory at Fort Knox, covered twenty-seven different foot measurements of 7,559 men. The other survey of nearly 100,000 men at separation centers was a part of an anthropometric survey conducted by the Quartermaster Corps.

During and since the war the Quartermaster Corps has supplied two hundred and thirty-nine different sizes of footwear in regular and special sizes, besides other sizes made to special measurements. There are ninety sizes in the regular footwear tariff. The one hundred and forty-nine special sizes covered men who could not be fitted in the regular tariff.

CHIEF DIETITIAN MADE A LIEUTENANT COLONEL

The Surgeon General announced February 24 the appointment of Major Helen C. Burns as assistant director of the new Women's Medical Corps and chief of the dietitian section of that corps, with the rank of Lieutenant Colonel, the highest grade yet held by an Army dietitian. Colonel Burns is a graduate of Simmons College, Boston, and attended the Army School for Dietitions at Walter Reed General Hospital. She was superintendent of dietitians in the Surgeon General's Office during the recent war and is a past president of the District of Columbia Dietetic Association.

AWARDS AND COMMENDATIONS

Colonel Montgomery E. Leary

The Army Commendation Ribbon has been awarded to Col. Montgomery E. Leary, M.C., O.R.C., of Rochester, N. Y. The citation reads as follows: "Colonel Montgomery E. Leary performed meritorious service as Contract Surgeon for the United States Army at Rochester, N. Y., from June 1943 to May 1945. Despite difficulties as to equipment, transportation, supplies and drugs necessary for the treatment of personnel at military installations in Rochester and the vicinity for whose care he was responsible, he displayed outstanding devotion to duty and loyalty in providing them with proper medical treatment and attention." Colonel Leary was graduated from the University of Pennsylvania Medical School and was called to active duty as medical officer in charge of medical care of personnel in the Rochester area June 1, 1943.

NAVY

APPROVED FOR POSTGRADUATE TRAINING

The Advisory Board of the Bureau of Medicine and Surgery has approved the following officers for postgraduate training:

Lieut. Frank H. Thomas Jr. (MC); course in internal medicine at the University of Pennsylvania Graduate School of Medicine.

Comdr. Henry J. Hunter (MC); obstetrics and gynecology at the Boston Lying-In Hospital and the Free Hospital for Women, Brookline, Mass.

Comdr. Clement D. Burroughs (MC); residency in ophthalmology at a Naval Hospital.

Lieut. (jg) Earl E. Correll (MC); residency in otolaryngology at the Naval Hospital, San Diego, Calif.

Lieut. David J. McMurray (MC); residency in otolaryngology at a Naval Hospital.

Lieut. (jg) Fred A. Valusek (MC); residency in otolaryngology at a Naval Hospital.

Lieut. (jg) Newman A. Hoopingarner (MC); residency in orthopedic surgery at Naval Hospital, St. Albans, L.I., N.Y.

Comdr. Richard B. Williams Jr. (MC); instruction in pathology and research at University of Pennsylvania.

Comdr. Neville C. Bowers (MC); additional years' training in psychiatry at National Naval Medical Center, Bethesda, Md.

Comdr. David P. Hightower (MC); additional years training in psychiatry at the Naval Hospital National Naval Medical Center, Bethesda, Md.

TRANSFER RESEARCH UNIT

The naval hospital at Dublin having been turned over to the Veterans Administration, plans are under way to transfer Naval Medical Research Unit 4 from that hospital to the Naval Training Station at Great Lakes, Illinois.

NAVY AWARDS AND COMMENDATIONS

Jacob C. Geiger, M.D.

The U.S. Navy, through the Surgeon General, has awarded a certificate of appreciation to Dr. J.C. Geiger, director of public health of San Francisco. The citation read as follows: "In grateful acknowledgment of exceptional and outstanding services rendered to the Medical Department of the Navy during the period of World War II." A special citation from the District Medical Officer of the Twelfth Naval District read: "For meritorious services in the control of communicable diseases in the port of San Francisco." Dr. Geiger graduated from Tulane University of Louisiana School of Medicine, New Orleans in 1912.

V 13
1948

VETERANS ADMINISTRATION

PATIENTS WITH NONSERVICE-CONNECTED DISABILITIES

In a statistical summary of Veterans Administration activities as of Jan. 3, 1948, the number of patients in hospitals was 109,018, of whom 94,948 were in veterans' hospitals. Of these, 62,384 were veterans with nonservice-connected disabilities and 31,297 were veterans with service-connected disabilities. Of the patients in other than veterans' hospitals, 8,085 were veterans with nonservice-connected disabilities and 5,953 were veterans with service-connected disabilities. In addition there were 14,920 beneficiaries in Veterans Administration homes. The number of veterans awaiting hospital admission at the end of the month was 19,505, of whom 18,907 had nonservice-connected disabilities.

NEW CHIEF OF NEUROPSYCHIATRIC SERVICE

Dr. Paul B. Magnuson, chief medical director of the Veterans Administration, has announced the appointment of Dr. Harvey J. Tompkins of Arlington, Va., as head of the neuropsychiatric service in the department of medicine and surgery to succeed Dr. Daniel Blain, who resigned to become medical director of the American Psychiatric Association. Dr. Tompkins graduated in medicine at Loyola University of Chicago. He joined the Veterans Administration in 1935 and, after serving at hospitals in various states, was assigned to the central office in 1945 as assistant chief of the neuropsychiatry division. He is associate professor in psychiatry at Georgetown University School of Medicine and is certified by the American Board of Psychiatry and Neurology.

PERSONAL

Dr. Lee G. Sewall has been appointed chief of professional services at the Roanoke (Va.) veterans' hospital and Dr. Victor J. Covalesky, as assistant chief.

Dr. Carroll L. Moore has become manager of the veterans' hospital at Excelsior Springs, Mo., succeeding Dr. S. E. Walker, who has been transferred to the regional office in Kansas City, Mo.

Dr. Peter A. Volpe, Worthington, Ohio, has been appointed medical director for the Veterans Administration for Ohio, Michigan and Kentucky. Dr. Volpe served in the recent war with the Sixth Armored Division.

MISCELLANEOUS

RADIOACTIVE ISOTOPES GO TO FOREIGN COUNTRIES

The United States atomic energy commission has disclosed according to *Chicago Tribune*, that forty-four shipments of radioactive isotopes have been sent to individuals and research groups in eight countries since the foreign distribution program was announced last September. Since then, sixteen countries have completed arrangements for receiving radioactive isotopes for medical and biologic research from Oak Ridge, Tenn. These countries are Argentina, Australia, Belgium, Canada, Cuba, Denmark, France, Ireland, Italy, Netherlands, New Zealand, Peru, South Africa, Switzerland and the United Kingdom. Radioactive phosphorus has been exported more than any other of the isotopes available.

Any country desiring radioactive isotopes must first submit to the state department the name of its representative in the United States who will maintain liason with the Atomic Energy Commission. The applicant country agrees to forward to the commission progress reports at intervals of six months on the results of the investigations carried on with the isotopes and agrees that the material will not be used for purposes other than those shown in the request.

ATOMIC ENERGY FELLOWSHIP TRAINING PROGRAM

The U. S. Atomic Energy Commission announces a fellowship program for training qualified persons for careers in the medical and biologic aspects of atomic energy. The commission will finance the program and establish the operating policies and training goals to be met; actual administration of the program, including selection of candidates, will be undertaken on behalf of the commission by the National Research Council, which has had broad experience in the administration of fellowship programs. Announcements concerning number of fellowships to be offered, stipends and qualifications of candidates and conditions of the awards will be issued through the National Research Council in the near future.

Applicants from any branch of biology or medicine are eligible for fellowships. At present, candidates will be favored who intend to follow a career of research in one of the basic biologic or medical sciences as related to the field of atomic energy or in clinical medicine or surgery as related to the field of atomic energy. Applicants in medicine and surgery will be encouraged to lay out a program of study leading to thorough experience in a preclinical science during which study they become identified with this science as such and not primarily with its application to clinical studies.

The initial fellowships will be distributed among three broad classes of candidates, including (1) doctors of medicine; (2) doctors of philosophy in the biologic sciences and (3) bachelors of science and of arts, who will receive training in health physics. Postdoctoral fellowships will extend for a period of two years with annual stipends, depending on marital status, commensurate with other fellowship programs. Graduate training in health physics will extend for a period of one year or longer, depending on the qualifications of the candidate and his need or desire for additional training.

It is anticipated that fellows trained under the program will become leaders in future development of medical and biologic education in the field of atomic energy. An opportunity to use their training at research and production centers will be offered, although the fellows will not be committed to work at installations of the Atomic Energy Commission following their training.

Special consideration will be given institutions in which it is possible to integrate medical and biologic training with physics, chemistry and mathematics. Since conditions allowing this combination are limited, special facilities are being provided at A. E. C. regional laboratories and at certain universities. However, fellowship training will not be limited to these institutions. As a rule a fellow will be requested to work in an institution other than that to which he is attached at the time of application or at which he has done most of his postgraduate work.

A paramount factor in planning the size and scope of the fellowship program was the serious shortage of trained scientific personnel in the field of atomic energy as applied to biology and medicine.

Medical News

(Physicians will confer a favor by sending for this department items of news of general interest: such as relate to society activities, new hospitals, education and public health. Programs should be received at least two weeks before the date of meeting.)

ALABAMA

First Annual Graves Lectures.—An annual lecture series honoring Dean Stuart Graves, director of admissions for medicine at the Medical College of Alabama, Birmingham, and dean of the school from 1928 to 1945, was initiated at the Jefferson-Hillman auditorium recently, sponsored by the Nu Sigma Nu Fraternity. Dr. E. Thompson Bell, director since 1921, department of pathology, University of Minnesota Medical School, Minneapolis, was the speaker. Dr. Graves has been a national officer of the Nu Sigma Nu Fraternity for more than forty years.

ARIZONA

Society News.—Dr. Charles N. Sarlin, Tucson, read a paper on "The Dissection of a Neurotic Personality" before the Arizona Society of Psychiatry and Neurology February 28.

Foods Manufacturer Fined.—A federal court jury February 20 found Adolphus Hohensee, lecturer on health and manufacturer of "Adolphus" brand foods and drugs, guilty on twenty-one of twenty-two counts charging misbranding of "health" products shipped in interstate commerce, according to newspaper reports. He was fined $1,800 and was not committed. Hohensee, a native of Scranton, Pa., had been lecturing in Phoenix.

CALIFORNIA

Popular Medical Lectures.—Stanford University School of Medicine, San Francisco, is presenting the sixty-sixth course of lectures at Lane Hall on Friday evenings at 8 o'clock. Three more lectures will be given: April 9, Drs. Roland A. Davison, Donald E. King and William H. Northway, all of San Francisco, "Rheumatism: the Great Crippler"; April 16, Dr. William M. M. Kirby, San Francisco, "Can Streptomycin Cure Tuberculosis?" and April 30, Dr. Edwin H. Lennette, Berkeley, "Filtrable Viruses: the Invisible Killers."

State Medical Meeting.—The annual session of the California Medical Association will be held in San Francisco with headquarters at the St. Francis Hotel April 11-14, under the presidency of Dr. John W. Cline, San Francisco. Guest speakers at the general sessions will be:

George F. Lull, Chicago, Secretary and General Manager, American Medical Association, What is Being Done About the Ten Point Program?
Richard B. Cattell, Boston, Carcinoma of the Rectum.
J. William Hinton, New York, End Result of Thorocolumbar Sympathectomy in Advanced Essential Hypertension.
Wesley Bourne, Montreal, Canada, Anesthesiology.
George W. Thorn, Boston, Diagnosis and Treatment of Adrenal Insufficiency.
Henry E. Michelson, Minneapolis, Dermatology.

A clinical-pathologic conference is scheduled for part of the Tuesday morning program, and special meeting on postgraduate training and medical economics will be held Wednesday from 2 to 4 p.m. Sectional meetings have been arranged on general surgery; general practice; anesthesiology; dermatology and syphilology; eye, ear, nose and throat; industrial medicine and surgery; neuropsychiatry; obstetrics and gynecology; pathology and bacteriology; pediatrics; public health; radiology, and urology. The Woman's Auxiliary will meet April 11-13 at the Mark Hopkins Hotel. The California Heart Association, the California Society of Internal Medicine and the Western Association of Industrial Physicians and Surgeons will hold annual meetings in conjunction with that of the medical association.

COLORADO

Course in Well Child Supervision.—The Colorado State Department of Health, the Rocky Mountain Pediatric Society and the University of Colorado Medical Center will sponsor a three day graduate course in well child supervision at the University of Colorado Medical Center, Denver, April 26-28. The course is intended primarily for Colorado physicians, but other physicians who are interested may apply in writing to the director of graduate medical education, Dr. Frode Jensen, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 7.

ILLINOIS

Meeting of Chest Physicians.—The Illinois Chapter of the American College of Chest Physicians will meet April 16 at 8 p.m. in the Congress Hotel, Chicago. Subjects to be discussed are "Bronchial Lavage as a Diagnostic Aid in Chest Diseases" and "Differential Diagnosis in Cystic Disease of the Lung." A panel discussion on adenoma of the bronchus completes the program. A dinner has been arranged at the hotel for 6:39 p.m., and all physicians are invited.

Chicago

Cancer Research Grants.—Grants totaling $325,547 for cancer research have been given to the University of Chicago and six individual medical investigators by the American Cancer Society, Inc. A check for $190,000 was received February 27 at the annual meeting of the cancer society in Chicago.

City Gets Third Cancer Detection Center.—The third cancer detection center for the city of Chicago was opened at Grant Hospital on March 12, under the sponsorship of the American Cancer Society Inc. Only women patients will be admitted. Other centers previously opened are at Women's and Children's Hospital and at Henrotin Hospital.

Kretschmer Memorial Lecture.—The seventh Edwin R. Kretschmer Memorial Lecture will be delivered at the Palmer House Friday evening, April 23, at 8 o'clock by Julius White, Ph.D., head chemist, U.S. Public Health Service, National Institute of Health, Bethesda, Md., on "Experimental Studies on Leukemia in Mice."

Northwestern Faculty-Alumni Reunion.—The annual Faculty-Alumni Reunion Dinner will be held May 8 at the Furniture Club of America, 666 Lake Shore Drive, Chicago, at 6 p.m. The cost of the dinner is $6 a plate, and reservations must be made not later than May 4 at the Medical Alumni Office, 303 East Chicago Avenue, Chicago, Room 796. The telephone number is Superior 4500. The five year classes of 1903, 1908, 1913, 1918, 1923, 1928, 1933, 1938 and 1943 should plan special reunions. The honored guests will be the fifty and fifty-five year classes, 1898 and 1893, and the graduating class of 1948. Special entertainment is being planned; there will be no speeches.

V 13
1948

IOWA

State Medical Meeting.—The Iowa State Medical Society will hold its ninety-seventh annual session at the Hotel Fort Des Moines, Des Moines, April 18-21 under the presidency of Dr. Harold A. Spilman, Ottumwa. Twelve guest speakers will give papers at the general sessions:

Howard B. Burchell, Rochester, Minn., Diagnosis of Congenital Heart Disease with Respect to Cardiac Catheterization and Oximetry.
John H. Moe, Minneapolis, Fractures of Neck of Femur.
Winthrop M. Phelps, Baltimore, Cerebral Palsy.
Charles D. May, Minneapolis, Chronic Disorders of the Digestive System in Children.
Walter C. Alvarez, Rochester, Minn., What Can the General Practitioner Do for the Nervous Patient?
W. Walter Wasson, Denver, The Lesser Circulation.
James S. Speed, Memphis, Tenn., Ruptured Intervertebral Disks.
Alson E. Braley, New York, Relation Between Ocular Disorders and Thyroid Dysfunction.
Willis J. Potts, Chicago, Diagnosis and Surgical Treatment of Patent Ductus Arteriosus and Congenital Vascular Ring.
Elmer L. Henderson, Louisville, Chairman, Board of Trustees, American Medical Association, World Medical Association.
M. Edward Davis, Chicago, Modern Management of Third Stage and Postpartum Hemorrhage.
Roland S. Cron, Milwaukee, Wis., Treatment of Carcinoma of the Cervix.

The annual banquet will be April 20 at 7 p.m. The Woman's Auxiliary to the society will meet April 19 and 20 at the Hotel Savery, and special luncheons and dinners have been scheduled for a number of state societies.

KANSAS

The Porter Lectures.—Dr. Chester S Keefer Boston; delivered the Porter Lectures March 39-31 at the University of Kansas School of Medicine Lawrence and Kansas City. His subjects were "Penicillin in the Medical and Surgical Practice," "Antibacterial Agents from Microbes" and "Streptomycin in the treatment of infections

Appoint Professor of Pathology. — Dr. Robert E. Stowell, formerly assistant professor of pathology at Washington University School of Medicine, St. Louis, has been appointed professor of pathology and oncology at the University of Kansas School of Medicine, Lawrence-Kansas City, effective March 1. Dr. Stowell received his M.D. degree from Stanford University School of Medicine, San Francisco, in 1941 and his Oh.D. degree from Washington University School of Medicine, where he has been on the staff since 1940.

MASSACHUSETTS

Nye Memorial Study.—The Massachusetts Division of the American Cancer Society, Inc. has granted Massachusetts General Hospital about $2,500, donated in memory of the late Dr. Robert N. Nye. The sum will be used to initiate and at least partly support the Robert Nason Nye Memorial Study. This study, a long-desired project of the x-ray department of the hospital where Dr. Nye served his internship, is concerned with the evaluation of changes in the peripheral blood correlated with known amounts of exposure to radiation sustained by the employees and staff of the x-ray department. Among other subjects to be studied is the incidence of leukemia among workers.

NEW YORK

Buffalo Alumni Clinical Day—The annual Clinical Day of the Alumni Association of the university of Buffalo School of Medicine, Buffalo, will be held April 17 at the Hotel Statler, Buffalo. Subjects under discussion include massive hemorrhage from peptic ulcer, management of gynecologic conditions, early recognition of pulmonary disease and diagnosis of respiratory symtoms in infancy. Class reunions will be held April 16 for the classes of 1883, 1888, 1892, 1898, 1903, 1908, 1913, 1923, 1928, 1933, 1938, and 1943.

New York City

Residencies Available.—The psychiatric division of the Kings County Hospital, Brooklyn, has a number of residents' positions available for appointment. This new psychiatric hospital is affiliated with the Long Island College of Medicine. Opportunities are available for degrees in graduate work during the residency. The standard resident's salary is $1,560 with maintenance. For information address the director of psychiatry, Dr. Sam Parker, Kings County Hospital, Albany Avenue and Winthrop Street, Brooklyn 3.

PENNSYLVANIA

Personal. — Dr. Charles C. Collester, Spencer, has retired from medical practice after thirty-five years of service to his community.

Society News.—At a meeting of the Reading Eye, Ear, Nose and Throat Society and the Diplomates Association of Berks County Physicians, Dr. Leandro M. Tocantins, Philadelphia, spoke on "The Critical Appraisal of Available Methods for the Control of Hemorrhagic States.

Philadelphia

Phi Lambda Kappa Lecture.—Dr. Lester R. Dragstedt Chicago, will deliver the second annual Phi Lambda Kappa Fraternity Lecture April 14 at 8:30 p.m in the Klahr Auditorium of thr Hahnemann Medical College on "Vatogomy in the treatment of Peptic Ulcer."

Dr. Long Receives Honorary Degree. — Dr. Esmond R. Long, director; Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis, University of Pennsylvania, received the honorary degree of doctor of science at a convocation in the various medical divisions of the university, March 6. Dr. Long has just returned from Germany, where he served on an Army commission for the study of tuberculosis in the American zone.

TENNESSEE

Annual Meeting of State Association.—The Tennessee State Medical Association will hold its annual meeting at the Maxwell House, Nashville, April 13-15 under the presidency of Dr. Franklin B. Bogart, Chattanooga. The tentative program lists the following guest speakers:

Axel N. Arneson, St. Louis, Prognosis in Carcinoma of the Uterine Cervix.
Byrl R. Kirklin, Rochester, Minn. Diaphragmatic Hernia.
Charles F. McKhann, Cleveland, Chronic Malnutrition in Children.
John Caffey, New York, Congenital Obstruction of the Alimentary Tract.
Fred V. Hein, Ph.D., Chicago, Physical Education and Athletics as Related to School Health.

The banquet in honor of President Bogart will be given April 14. Mr. Mac F. Cahal, Chicago, will speak on "Caution! Curves Ahead." The Woman's Auxiliary will meet April 13-15 with headquarters at the Hermitage.

TEXAS

Lectures by Dr. Best.—Dr. Charles H. Best, Toronto, Canada, delivered the annual Phi Beta Pi Lecture at Baylor University College of Medicine, Houston, March 22 on "The Pancreas as the Guardian of the Liver"; on March 25 he delivered the Albert Surman Memorial Lecture under the auspices of Phi Beta Pi Medical Fraternity at the University of Texas Medical Branch, Galveston. He also gave a series of four lectures on the physiology of carbohydrate and fat metabolism at Baylor University during the week.

Conference Pediatric.—A Pediatric postgraduate conference will be held at the University of Texas School of Medicine, Galveston, April 12-17 under e auspices of the university's Child Health Program and in cooperation with the Maternal and Child Health Division of the Texas State Board of Health. The subjects of the program on Monday will be the problem of infantile diarrhea and heart disease; on Tuesday poliomyelitis, and physiology of the newborn; on Wednesday, speech and speech correction; on Thursday, infant feeding and infectious diseases (continued) and on Saturday papers will be presented on adenoid pathology, deafness and acute poisonings.

WEST VIRGINIA

Meeting on Industrial Medicine.—A meeting, of physicians and nurses engaged in industrial work, sponsored by the industrial committee of the Kanawha Medical Society, will be held at the Ruffner Hotel in Charleston April 11. Sessions will begin at 10:20 a.m. The program follows:

Ralph S. McLaughlin, Charleston, Chemical Injuries to the Eye.
E. Hunter Boggs, Charleston, Industrial Skin Lesions.
Theodore P. Mantz, Charleston, Methods of Skin Grafting.
Walter G. Putschar, Charleston, Dangers and Pitfalls in Intravenous Medication.
J. Huber Wagner, Pittsburgh, Present Treatment of Wounds.
Bert Bradford Jr., Charleston, Treatment of Abdominal Injuries.
Henry M. Escue, Charleston, W. Va., Treatment of Urinary Bladder and Urethral Trauma.

Dr. J. Huber Wagner, Pittsburgh, will meet with members of the college at noon to discuss organizational matters.

WISCONSIN

Cancer Symposium in Milwaukee.—The Medical Society of Milwaukee County and the Milwaukee Division of the American Cancer Society, Inc. will present their second annual Cancer Symposium April 8-9 in Milwaukee. A clinic will be held at the Milwaukee Cancer Detection Center, and an address will be given at Marquette University School of Medicine auditorium at 8 p.m. followed by a panel discussion on "Management of the Late Cancer Patient". After the clinic group meeting at the Milwaukee County Hospital April 9 the following program, to be given at 2 p.m., has been arranged:

Arthur C. Allen, New York, Practical Fundamentals of the Nevi and Melanoma Problems.
J. Barrett Brown, St. Louis, Cancer of the Lip and Mouth.
Leon Schiff, Cincinnati, When Does Jaundice Mean Cancer?
Vernon C. David, Chicago, Indications for Surgical Procedures in Cancer of Rectum.

At 2 p.m. April 10 Dr. Allen will conduct a slide seminar on dermatologic lesions. All interested physicians are invited to attend.

GENERAL

Annual Specialists' Meeting.—The American Laryngological, Rhinological and Otological Society, Inc. will hold its annual meeting April 7-9 at Chalfonte-Haddon Hall, Atlantic City, N. J., under the presidency of Dr. Lyman G. Richards, Brookline, Mass. Physicians invited to take part in discussions include Arthur M. Olsen, Rochester, Minn.; Hallowell Davis, St. Louis; Stuart C. Cullen, Iowa City, and Morris Fishbein, Chicago.

Students International Clinical Congress. -- The International Union of Students and the British Medical Students Association invites a delegation of fifteen medical students from the United States to a Students' International Clinical Congress of two hundred delegates in England July 6-24, 1948. Lectures and clinical teaching will be held in London, Oxford and Birmingham. Transportation and housing will be arranged at minimal expense. For information write Anna P. Cort, Chairman, Committee on International Teaching Congress, AIMS, Boston University School of Medicine, 80 East Concord Street, Boston.

Southeastern Surgical Congress.—The sixteenth annual postgraduate assembly of the Southeastern Surgical Congress will be held in Hollywood, Fla., April 5-8 at the Hollywood Beach Hotel, under the presidency of Dr. Herbert Acuff. The papers to be presented are intended to make up an inclusive refresher course. The C. Jeff Miller Lectureship will be presented Monday, 8 p.m., by Dr. R. L. Sanders, University of Tennessee College of Medicine, Memphis, on "Palliative Treatment for Carcinoma of the Pancreas." The Southeastern Surgical Congress recently purchased the old John P. Huntley home, 1439 Peachtree Street, Atlanta, Ga., as general headquarters for the congress.

Meeting of Laryngological Association.—The annual meeting of the American Laryngological Association will be held at the Homestead, Hot Springs, Va., April 14-15 under the presidency of Dr. Arthur W. Proetz. St. Louis Physicians presenting papers by invitation are:

Harold I. Lillie and Clifford F. Lake, Rochester, Minn., Mucoceles, Pyoceles and Cystic Degenerative Lesions of the Mucous Membrane of the Frontal and Ethmoidal Paranasal Sinuses.
Ko K. Chen, Indianapolis, Aliphatic Versus Aromatic Amines as Vasoconstrictors.
Edwin N. Broyles and Edward M. Walzl, Baltimore, Postoperative Course of Subperichondral Total Laryngectomies.

The president's reception at 6 p.m. April 14 will be followed by the annual banquet for fellows only.

MARRIAGES

JOHN KINGSLEY LATTIMER to Miss Jamie Elizabeth Hill, both of Jackson Heights, N.Y., January 23.

HERMAN N. EISEN, Brooklyn, to NATALIE ARONSON of New York, in February.

HARRISON CLINTON FLOURNOY, Warwick, Ga., to Miss Altalene Ethel Russell of Eufaula, Ala., in Shellman, Ga., February 2.

CRAIG WILLIAMSON, Upland, Calif., to Miss Betty Lucile Payne of Los Angeles.

JAMES SAMUEL GARNER Jr., Plant City, Fla., to Miss Mary Elizabeth Arnold of Washington, D.C., at Falls Church, Va., February.

JOHN JOSEPH McGILLICUDDY, Lynn Mass., to Miss Mary Louise Godvin of Orange, N.J., at Chestnut Hill, Mass., recently.

GEORGE LEGARE KERRISON to Miss Mildred Virginia Burdashaw, both of Charleston, S.C., February 10.

V 13 1948

Deaths

Gilbert Seymour Osincup ⊕ Orlando, Fla.; born in Cedar Rapids, Iowa, Jan. 17, 1894; University of Tennessee College of Medicine, Memphis, 1916; past president of the Florida Medical Association and of the Orange County Medical Society; fellow of the American Academy of Pediatrics; specialist certified by the American Board of Pediatrics; served with a British infantry regiment and the Royal Air Force during World War I and was decorated by King George V of England with the British Military Cross; in 1946 retired as senior surgeon, U. S. Public Health Service reserve, and during World War II served in the European and Middle Eastern theaters of operation, assigned to British Occupational Forces in Greece; formerly served on the Florida Defense Council as chairman of health and housing and as chairman of selective service for Orange County; received the certificate of honor from the Florida Medical Association and the Selective Service Medal from President Truman; served as president of the medical staff of Orange Memorial Hospital, where he had been chief of the pediatric service for many years; died Nov. 26, 1947, aged 52, of carcinoma of the lungs.

Fred Towsley Murphy, Grosse Pointe, Mich.; born in Detroit Oct. 23, 1872; Harvard Medical School, Boston, 1901; at one time on the faculty of his alma mater and professor of surgery at the Washington University School of Medicine in St. Louis; member of the American Medical Association, serving as a delegate from Massachusetts in 1911; member of the Massachusetts Medical Society, American Surgical Association and the Society of Clinical Surgery; fellow of the American College of Surgeons; member of the founders group of the American Board of Surgery; during World War I a commanding officer of Base Hospital 21 in France; awarded the Distinguished Service Medal for supervising evacuation of First Army casualties, and later became director of medicine and surgery for the American Red Cross; in 1921 became a brigadier general in the U.S. Army reserve; at one time on the staffs of the Infants' Hospital in Boston and the Barnes Hospital in St. Louis; member of the board at Harper Hospital in Detroit; a trustee of Phillips Andover Academy in Andover, Mass.; died January 10, aged 75, of bronchopneumonia.

Archibald Alexander MacLachlan ⊕ Pittsburgh; born in Claysville, Pa.; in 1874; University of Pennsylvania Department of Medicine, Philadelphia, 1900; served on the faculty of the University of Pittsburgh School of Medicine; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology and of the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; affiliated with the Eye and Ear and Southside hospitals; died at his home in Library, Pa., Dec. 2, 1947, aged 73.

Joseph Moses Jr., Northfield, Minn.; born in Herman, Minn. Nov. 17, 1887; University of Minnesota Medical School, Minneapolis, 1914; member of the American Medical Association; past president of the Rice County Medical Society; served during World War I; chairman of the Rice County Public Health Association, and during World War II served as medical examiner for war services; member of the board of education; vice president of the Northfield National Bank; died recently, aged 60, of coronary thrombosis.

Charles Fisher Lippe, New York; New York University College of Medicine, 1939; diplomate of the National Board of Medical Examiners; served as a lieutenant commander in the medical corps of the U. S. Naval Reserve during World War II; resident at Veterans Administration Hospital in Fort Logan, Colo.; interned at the Hospital for Joint Diseases in New York; formerly resident at Sea View Hospital in Staten Island and Mount Sinai Hospital in New York; died recently, aged 33, of coronary disease.

George Everet Alexander, Castle Rock, Colo.; University of Buffalo School of Medicine, 1885; member of the American Medical Association; served as county health officer; died recently, aged 88.

Joseph Long Alexander, Staunton, Va.; University of Virginia Department of Medicine, Charlottesville, 1900; member of the American Medical Association; affiliated with the Kings' Daughters' Hospital, where he died Dec. 16, 1947, aged 70, of chronic myocarditis.

Clayton Witters Bartlett, Bennington, Vt.; University of Vermont College of Medicine, Burlington, 1888; member of the American Medical Association; fellow of the American College of Surgeons; died Dec. 23, 1947, aged 82, of arteriosclerotic heart disease.

William Alonzo Bockoven ⊕ Cresco, Iowa; State University of Iowa College of Medicine, Iowa City, 1921; fellow of the American College of Surgeons; member of the school board; affiliated with Decorah Hospital in Decorah and St. Joseph Mercy Hospital; died Dec. 30, 1947, aged 53, of coronary thrombosis.

James Marshall Braden, Lafayette, Colo.; Hospital College of Medicine, Louisville, Ky., 1891; at one time health officer of Carbondale; served during World War I; twice mayor of Lafayette; died in the Community Hospital, Boulder, Nov. 29, 1947, aged 79.

Edgar Marx Braun, Irvington, N. J.; Duke University School of Medicine, Durham, N.C., 1936; member of the American Medical Association; diplomate of the National Board of Medical Examiners; died in East Orange Dec. 26, 1947, aged 38, of coronary occlusion.

William O. Burbank, Gaines, N.Y.; University of Buffalo School of Medicine, 1889; formerly a member of the school board, health officer and coroner of Pavilion; died in St. Jerome Hospital, Batavia, Dec. 24, 1947, aged 87, of arteriosclerosis and bronchopneumonia.

William Alvin Camp ⊕ Cullman, Ala.; Emory University School of Medicine, Atlanta, 1941; interned at the Employees' Hospital of the Tennessee Coal, Iron and Railroad Company in Fairfield; served during World War II; affiliated with the Cullman Hospital; died Nov. 29, 1947, aged 32, of coronary thrombosis.

Benjamin L. Carter, Covington, Va.; Baltimore Medical College, 1893; member of the American Medical Association; served as secretary of the Alleghany County Board of Health; chairman of the board of directors of the Citizens National Bank; died Dec. 7, 1947, aged 82, of coronary thrombosis.

Andrew Jackson Cooper, Midland, Texas (licensed in Texas under the Act of 1907); member of the American Medical Association; during World War I on the examining board of Taylor County, where he had been county health officer; at one time served as local surgeon for the Missouri, Kansas and Texas and the Frisco railroads; died Dec. 24, 1947, aged 72, of cardiovascular disease.

Noah Albert Davidson, Harlingen, Texas; Baylor University College of Medicine, Dallas, 1911; member of the American Medical Association; died Dec. 10, 1947, aged 66.

Roy Edgar Emanuel ⊕ Chickasha, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1926; served as vice president of the Oklahoma State Medical Association; affiliated with the General Hospital; died Dec. 6, 1947, aged 46, in an airplane accident.

Jack Albert Churchill King, Vevay, Ind.; University of Michigan Medical School, Ann Arbor, 1933; member of the American Medical Association; past president of the Switzerland County Medical Society; died Dec. 6, 1947, aged 41.

John Elwood Knight ⊕ Warrenton, Va.; Medical College of Virginia, Richmond, 1908; formerly vice president of the Medical Society of Virginia; served as vice president of the Fauquier County Medical Society; died Dec. 30, 1947, aged 64, of heart disease.

Arthur Dillard Harmon Little, Thomasville, Ga.; Medical Department of Tulane University of Louisiana, New Orleans, 1908; member of the American Medical Association and of the Southeastern Surgical Congress; fellow of the American College of Surgeons; for many years a member of the board of education; served during World War I; affiliated with the Archbold Memorial Hospital, where he died recently, aged 66, of coronary thrombosis.

Clarence Homer Lefever, Erie, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1902; member of the American Medical Association; past secretary and president of the Erie County Medical Society; chief of medical service at St. Vincent's Hospital, where he died January 11, aged 73, of a fracture of the vertebrae and subacute lateral sclerosis.

Benjamin Meyer Levine, Forest Hills, N. Y.; Columbia University College of Physicians and Surgeons, New York, 1906; member of the American Medical Association; died recently, aged 62, of coronary disease.

Daniel W. Lowe, Woodsfield, Ohio; Starling Medical College, Columbus, 1903; member of the American Medical Association; formerly county health commissioner; died Dec. 2, 1947, aged 72, of heart disease.

Joseph Luff, Independence, Mo.; Kansas City (Mo.) Hahnemann Medical College, 1903; also a minister; died January 6, aged 95.

Bernard Norton MacLafferty, Malone, Wash.; American Medical Missionary College, Battle Creek, Mich., and Chicago, 1904; died Dec. 8, 1947, aged 69, of coronary thrombosis.

John Archibald MacMillan, Brookline, Mass.; Hahnemann Medical College and Hospital of Philadelphia, 1906; formerly assistant professor of clinical dermatology at the Boston University School of Medicine; member of the New England Dermatological Society; died Dec. 19, 1947, aged 64, of cerebral hemorrhage.

Fred Wasco Maxey, Superior, Neb.; Central Medical College of St. Joseph, Mo., 1905; veteran of the Spanish-American War; died Dec. 7, 1947, aged 71.

Charles C. Meade, Cincinnati; Pulte Medical College, Homeopathic, Cincinnati, 1890; died recently, aged 85.

Clarence Beacom Millhoff ⊕ Johnstown, Pa.; Jefferson Medical College of Philadelphia, 1897; died recently, aged 74.

George A. Morley, Crookston, Minn.; Rush Medical College, Chicago, 1897; past president of the public school system; member of the American Medical Association and of the American Academy of Ophthalmology and Otolaryngology; specialist certified by American Board of Ophthalmology; affiliated with Bethesda and St. Vincent's hospitals; died recently, aged 79, of heart disease.

Ernst R. Schoen, Jackson, Mo.; Homeopathic Medical College of Missouri, St. Louis, 1895; member of the American Medical Association; died Nov. 23, 1947, aged 74, of cerebral hemorrhage.

Christian Ulrich Senn ⊕ Ripon, Wis.; Wisconsin College of Physicians and Surgeons, Milwaukee, 1906; served during World War I; examining physician for the Selective Service Board during World War II; affiliated with Ripon Municipal Hospital, where he died Nov. 28, 1947, aged 69, of cerebral hemorrhage.

Walter Lewis Tanner, Newark, N. J.; Boston University Medical School, 1919; found dead in Philadelphia Dec. 16, 1947, aged 54.

Ralph Waldo Thompson Cornwall-on-the Hudson, N.Y.; New York Homeopathic Medical College and Flower Hospital in New York, 1908; health officer; died January 12, aged 71, of carcinoma.

Charles Burleigh Thomas, Cleveland; Cleveland Medical College, Homeopathic, 1891; served in France during World War I; died in East Cleveland Dec. 30, 1847, aged 81.

James Edward Trotman, Oklahoma City, Okla.; Meharry Medical College, Nashville, Tenn., 1936; died in the Massachusetts Memorial Hospital, Boston, Dec. 17, 1947, aged 49, of rapidly progressive hypertension.

William Miles Wallis Maryville, Mo.; Central Medical College of St. Joseph, Mo., 1903; served during World War I; affiliated with St. Francis Hospital; died Dec. 12, 1947, aged 67, of myocarditis.

Albert Davis Webb, Williamstown, Ky.; Medical College of Ohio, Cincinnati, 1886; also a druggist; died Dec. 19, 1947, aged 85, of pneumonia.

Hyman Wechsler, Los Angeles; Medical College of Indiana, Indianapolis, 1883; died recently, aged 90.

Edgemont David Welsh, Grand Rapids, Mich.; Michigan College of Medicine and Surgery, Detroit, 1905; died Dec. 5, 1947, aged 63, of coronary thrombosis.

Edward Augustus Williamson, Stamford, Conn.; Bellevue Hospital Medical College, New York, 1886; served during World War I; member of the staff of Stamford Hospital, where he died January 6, aged 83, of a fractured hip and hypostatic pneumonia.

Thomas Valentine Williamson, Norfolk, Va.; University of Virginia Department of Medicine, Charlottesville, 1908; served during World War I; affiliated with the Norfolk General and Leigh Memorial hospitals; died Dec. 29, 1947, aged 63, of heart disease.

Leon Gilbert Woodford ⊕ Everett, Wash.; Denver and Gross College of Medicine, 1909; fellow of the American College of Chest Physicians; formerly city physician; chairman of the advisory board of the Salvation Army; affiliated with Everett General Hospital and Providence Hospital, where he died Dec. 28, 1947, aged 65, of hypertension and cardiovascular renal disease.

V 13
1948

Foreign Letters

PARIS

(From Our Regular Correspondent)

Feb. 27, 1948.

Public Health in France Since the Liberation

In a press conference of January 15, Dr. Cavaillon general director to the Ministry for Public Health and Population, emphasized that, though being less serious than in 1943 and 1944, the situation with regard to public health has not improved greatly since 1946. Health examinations of school children and adolescents show many deficiencies resulting from undernourishment due to food shortages

Epidemic Diseases Under Control

Since 1945, there have been only 395 cases of exanthematous typhus, all but four or five in prisoners or deportees returning from Germany. A small outbreak of plague (13 cases) was rapidly checked by vaccination of the inhabitants of Ajaccio. Scarlet fever was reduced from 30,000 cases in 1946 to 4,000 in 1947, and measles from 30,000 in 1946 to 16,000 in 1947. Diphtheria was increased from 17,000 cases in 1938 to 45,000 in 1945, and then reduced to 9,700 in 1947. Poliomyelitis was reduced to 1,148 cases in 1947 and 46 cases of smallpox occurred. No case of cholera was imported to France from epidemic areas in Asia. Syphilis is also showing notable decrease.

Tuberculosis

In 1947 figures for tuberculosis were the lowest ever recorded, 89 cases per hundred thousand inhabitants. Numerous deaths during the occupation reduced the global number of patients with active infection; nevertheless, there is a decrease due to early detection, isolation of the patient and treatment. Tuberculosis is still serious because of underfeeding in cities, the difficulty of obtaining sufficient food in sanatoriums and the present impossibility of expanding sanatorium facilities.

Infant Mortality

Infant mortality increased during the war and the occupation, reaching a maximum in 1945 with a rate of 10.8 per cent. Regression is noted for 1947 (6.5 per cent). This rate is still high compared with that of other countries, as nearly 100,000 children under 1 year of age die every year in France. Results are due to a large number of medical and sanitary conditions, most of which can be corrected. Improvement is expected in the coming year.

General Mortality

The prewar mortality rate in France was 1.57 per cent; it rose to 2.04 in 1944 and dropped to 1.34 in 1947. France as a whole requires continued improvement of health measures and war increased the need for better sanitary facilities and equipment. Thirteen new hospitals are now under construction and others, which were in course of construction before the war, will soon be finished.

Death of Philippe Pagniez

Philippe Pagniez died at the age of 74. As a Member of the National Academy of Medicine, he took part in the scientific direction of *La presse medicale*. Dr. Pagniez's main work, in the field of neurology, is epilepsy; in his famous book on that subject he brought to the fore the two factors, one nervous, the other humoral, which intervene in the pathologic processes of this disease. By patient research and observation he demonstrated the modification in the composition of the blood in epileptic persons, modifications brought about by a hemoclastic crisis-anaphylactic shock, which can set off authentic convulsive paroxysms. He discovered the essential cause of the guinea pig's epilepsy, described by Brown-Sequard. Pagniez is well known for his hematologic work, including that on hemolysins and agglutinins. His work in the fields of allergy and anaphylaxis has contributed greatly to the solution of the problem of allergy of the digestive tract. With Pasteur Vallery-Radot, he has shown the part played by the humoral imbalance in the genesis of migraine.

Miscellaneous

Professor B. Houssay, of Buenos Ayres, Doctor Honoris Causa of the Paris University, Nobel prize winner, delivered a lecture at the Paris Faculty of Medicine on experimental diabetes. Professor E. Cruz-Coke of Santiago, recently made Doctor Honoris Causa of the Paris University, delivered a lecture on arterial hypertension of renal origin at the Paris Faculty of Medicine.

The Medical Days of the Propedeutic Clinics of the Broussais Hospital will take place in Paris, May 21-23 under Professor Pasteur Vallery-Radot. For information apply to Professor J. Hamburger, 29 Boulevard de Co ccelles, Paris.

The First International Congress on Surgical Films, organized by "Art and Science", took place in Paris, April 7, 1948, at "Mutualite" Palace.

BELGIUM

(From Our Regular Correspondent)

Feb. 28, 1948.

Biliary Radiomanometry

At the Belgian Society of Gastroenterology, Caroli of Paris presented his six years' experience with radiomanometry, which combines the technics to measure the pressure necessary for the perfusion of the biliary passages when drains have been placed after surgical intervention and those which are used for contrast mediums that are introduced for the radiographic study of the biliary passages.

The author employs "tenebryl" (aiodine (preparation) as a contrast medium. The zero point of the manometer is placed on the level of the choledochoduodenal juncture. He visualizes the introduction of the contrast liquid in the gallbladder, measures the pressure of filling of the latter and takes a picture. Then he measures the pressure necessary to pass the sphincter of the gallbladder; this pressure varies between 12 and 14 cm. of water.

In the normal subject, as soon as the sphincter of the gallbladder is passed, the biliary tree is filled without stoppage up to the duodenum. When the biliary tree is thus filled, it is advisable to take serial pictures. One sees then the movements of closing and opening of the sphincter of Oddi, giving rise to veritable ejaculations of contrast liquid into the duodenum. The pressure required to pass this choledochoduodenal juncture is between 10 and 12 cm. of water, that is to say, lower than that required for the passage of the vesical sphincter. If it is necessary to reach a pressure of 20 cm. of water and more, it is an indication of an organic lesion and if instead of employing surgical treatment only a cholecystectomy is made, the latter will be followed by pain.

Correspondence

MALIGNANT EXOPHTALMOS

To the Editor:—In view of the general air of pessimism which permeates the approach to malignant exophthalmos, an attitude shared by your contributor Dr. Willard O. Thompson (THE JOURNAL, January 31, p. 314) in his recent delightful article, perhaps it is worth while briefly to record 2 cases of successful treatment.

The first patient was a Royal Air Force flight sergeant pilot aged 28, who eight years before had had an operation for a large simple goiter. He was referred for increase in weight, shortness of breath, lethargy, slowing of thought and moderate exophthalmos. He presented classic features of early myxedema: a skiagram of the chest showed tracheal compression from a substernal goiter: the goitrous mass was resected and thyroid sicca (B.P.) ½ grain (0.03 Gm.) three times a day and Lugol's solution 5 minims (0.31 cc.) three times a day were prescribed. His general condition improved immensely: the exophthalmos receded rapidly, and within three months of his first being seen he was considered fit enough to return to operational flying duty. Unfortunately, the exigencies of the service prevented full follow-up, but when last seen he was well and symptom free, taking 1½ grains (0.10 Gm.) of thyroid sicca daily.

The second patient was a girl aged 19 who was referred with a presumptive diagnosis of exophthalmic goiter. She had suffered from bronchial asthma since childhood and had always been of nervous disposition. There was moderate exophthalmos: the thyroid was diffusely enlarged to about thrice its normal size, and there were pronounced tremors of the extended fingers. She had, however, recently gained weight and the hands, even on a warm day, were abnormally cold. Psychologic history revealed personality inadequacy with fairly severe emotional conflicts and features of chronic anxiety. Accordingly the diagnosis was "chronic anxiety state with hypothyroidism and thyrotropic exophthalmos". She was admitted to hospital and given thyroid sicca 5 grains (0.32 Gm.) three times a day and Lugol's iodine 5 minims (0.31 cc.) three times a day. Within a week the exophthalmos had noticeably diminished and the thyroid had reverted almost to its normal size and consistency. Shortly afterward, she was discharged to outpatient care and seen at regular intervals, continuing to take 1 grain (0.06 Gm.) of dried thyroid daily. A year after her first being seen the eyes were only slightly prominent, and no abnormality of the thyroid was palpable. Further, her asthmatic attacks were much diminished in severity and frequency. Her dose of thyroid sicca had now been reduced to ½ grain (0.03 Gm.) daily and the iodine had been omitted.

Both of these patients were seen within a few days of their first noticing the prominence of the eyes, and in both treatment was begun early. This may account for the good results obtained and should encourage one to bear this possible diagnosis in mind when seeing cases which at first sight suggest Graves' disease, diffuse goiter with hyperthyroidism. The second patient had already been seen by several physicians who had accepted the diagnosis of primary thyrotoxicosis. It is probable that, if corresponding lines of treatment had been followed, the ultimate results would not have been so good. As it was, the final outcome in both instances should perhaps encourage us to discard the rather terrifying name which has been attached to this condition.

J. DONALDSON CRAIG, M.D.
72 Westbourne Terrace,
London W. 2, England.

NOTE ON THE INCEPTION OF THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES

To the Editor:—In 1890 while studying abroad I received letters from my father, Dr. Aaron Friedenwald, professor of ophthalmology in the College of Physicians and Surgeons of Baltimore. The following excerpts throw an interesting light on the creation of the Association of American Medical Colleges.

Excerpt from letter dated Jan. 30, 1890:

> Dr. Cordell has stirred up the profession in Baltimore in reference to the Colleges' raising their standard. The University of Maryland a few weeks ago announced that from the next session a compulsory three year graded course would be adopted. Dr. Latimer and I were appointed a committee to represent the College of Physicians and Surgeons at a meeting (of the faculty) held last week. I took the ground that the simple adoption of a three years' course by the colleges of this city might not accomplish at all what the profession seemed so much to desire. I could imagine a result which would attract the students, who would be prevented by such an action to come to Baltimore, to colleges whose requirements were not so high. In such a case, the profession at large would not be benefited, but very probably the college might be made to suffer to an extent that would greatly endanger its existence. I therefore preferred that a circular should be sent to all colleges of the United States having a two years' course (asking them) to send delegates to the meeting to take place in Nashville (Tenn.) in May next, when the American Medical Association will meet there, for the organization of an Association of American Medical Colleges, whose purpose it shall be to elevate the standard by a concert of action; the delegates sent to this meeting to be instructed to vote for a three year graded course. I think the time an opportune one to bring about this result. It is true that a similar effort ended in failure about twelve years ago. The *vis c tergo* in the shape of the state medical examinations, which so many states have adopted, did not exist at that time, and it seems to me the best way out of the difficulty. My proposition met with favor, and tomorrow there will be another meeting to consider the circular, the preparation of which has been entrusted to Dr. Cordell. If this effort will be successful, it will be a great achievement, and our college will have the credit of first proposing a practical method of disposing of this vexed question.

Excerpt from letter dated Feb. 9, 1890:

> On last Thursday a meeting of the representatives of the various medical colleges in Baltimore took place and my proposition to send a circular to all medical colleges in the United States for a meeting in Nashville in May, to raise the standard of medical education by a concerted movement, was adopted. I hope that this will lead to something.

The call for the meeting went out over the signatures of A. Friedenwald, chairman, and E. F. Cordell, secretary. The former was elected vice chairman of the newly formed association.

HARRY FRIEDENWALD, M.D., Baltimore.

V 13
1948

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Food and Drug Acts: Evidence of Misbranding of Device.—The United States filed a libel against sixteen Sinuothermic machines, owned or manufactured by the claimant, on the ground that they were misbranded when shipped in interstate commerce. The misbranding was alleged to have consisted of printed matter accompanying them which represented that the machines had a therapeutic value in the diagnosis and treatment of stated diseases of man, whereas the devices were not effective for such purposes. From a judgment of condemnation and destruction, the claimant appealed to the circuit court of appeals, fifth circuit.

The federal law prohibits the introduction into and the receipt in interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded and provides for seizure and condemnation of such. It is not denied that these machines were devices within the act. A drug or device shall be deemed to be misbranded, within the federal act, if its labeling is false or misleading in any particular. The term "labeling" means all labels and other written, printed or graphic matter on any article or any of its containers or wrappers or accompanying such article. The last three words, said the court of appeals, are critical here. They make the term "labeling" broader than "label," which includes only what is displayed on the immediate container of an article. How much broader? The sixteen devices in question were shipped in several consignments from a place in Florida to a designated place in Ohio. The first three shipments went forward and were received by the proper party and put to work in his medical practice several weeks before any leaflets were sent. They did not accompany any of the devices while they were in interstate commerce. The last of the shipments went forward three weeks after the leaflets and was not accompanied by them. Accompany, said the court, means to go along with. In a criminal and forfeiture statute the meaning cannot be stretched. Furthermore, it may be doubted, said the court, that the printed matter is in its nature a labeling for the machines. It looks like a small newspaper, entitled "The Road to Health, by Dr. Fred Urbeteit. Every subject pertaining to Health, Doctoring and Nursing is being taught at the College of Sinuothermic Institute, Inc., 307 West Euclid Ave., Tampa, Florida." To the left of this heading is a picture of Dr. Fred Urbeteit, president of Sinuothermic Institute, Inc., and to the right an attractive picture of the institute and its grounds. Fifteen columns of fine print are below, consisting of testimonials and case histories of patients who had been treated at the institute by Dr. Urbeteit, with unstinted praise of both. The Sinuothermic machine is mentioned and praised as an instrument of diagnosis and treatment, but there is no description or picture of the machine, no explanation of its operation and no suggestion that it is for sale. The whole thing, said the court of appeals, appears to be an advertisement for the institute and Dr. Urbeteit, rather than something to accompany machines. Whether we ought to hold it a labeling of these machines if shipped simultaneously with them, the court continued, may be doubted. But if it could be called labeling, it is not proved by the present skimpy evidence that it accompanied the machines or any one of them while they were in interstate commerce.

The claimant vigorously contended that all he had said in "The Road to Health" was true. He offered in his claim, since no employee of the United States and only a few practitioners whom he had instructed, had any actual knowledge of his machine, to conduct a series of tests of it in cooperation with practitioners of medicine, osteopathy, chiropractic and naturopathy approved by the court, preferably on persons previously treated by medical practitioners without success, they to be examined before and after the test by physicians appointed by the court during such period as the court should fix, the physicians' determination of the results to be evidence in the case. This was not done. Dr. Urbeteit at least seems convinced of the efficacy of his machine, said the court of appeals. He testified in detail as to each case mentioned in "The Road to Health." He had present 30 of his patients, whom he offered as witnesses to the benefits they had received, many of them being those mentioned in "The Road to Health." The trial judge refused to hear them on the ground that, being laymen, they could not testify as to what was the matter with them and consequently could not say what they were relieved from, and that the diagnoses testified to by Dr. Urbeteit could not be accepted because he rested them on the use of his machine which the government's witnesses, who were men of high standing in medicine and in the electrical arts, had testified could not do what Dr. Urbeteit claimed. These rulings, said the court of appeals, were error. One was based on the idea that Dr. Urbeteit had made his diagnoses solely on the indications of the machine. But his testimony as a whole was that he used all known methods of diagnosis, that the machine did not indicate any particular disease but only located the spot where the abnormal tissue was, and that it was then a matter of judgment as to what the disease was. He only claimed the machine to be an aid in diagnosing. The patients themselves, said the court, could certainly know whether their external symptoms abated and their pains ceased. Urbeteit, being a licensed doctor of some twenty years' practice, could express expert opinions. The judge might, continued the circuit court of appeals, after hearing all the evidence, prefer the expert opinions of the government witnesses to those of Dr. Urbeteit, even as against the facts to which he and his witnesses might swear, but the judge should have heard all the competent testimony before making up his mind. The most eminent physicians and scientists have in the past erred in their opinions, and opinions generally must yield to well proved contrary facts. The case, the court concluded, ought to have been more fully tried. Accordingly, the judgment in favor of the government was reversed and the cause was remanded for further proceedings.—*Urbeteit v. United States, 164 F. (2d) 245 (1947).*

Medical Motion Pictures

NEW MOTION PICTURE ADDED TO A.M.A. LIBRARY

Surgery in Chest Diseases, 16 mm., black and white, sound, 1,400 feet (one reel), showing time forty-five minutes. Prepared in 1945 for the British Ministry of Information, London, England. Produced by G. B. Instructional, Ltd., London. Procurable on loan from the American Medical Association, Committee on Medical Motion Pictures, 535 North Dearborn St., Chicago, 10.

This motion picture portrays the diagnostic, surgical and rehabilitation technics in a large hospital for diseases of the chest. In particular, it follows one patient through all these procedures from the time that a cancer of the lung is recognized on a routine roentgen examination of the chest until he returns to work on an occupation suited to his convalescent regimen. This patient was in the hospital many weeks longer than necessary. Much of this time could well have been spent at home; his rehabilitation could have been conducted in an outpatient clinic and in various normal activities as well as in rehabilitation hospitals and elaborate occupational therapy shops.

Throughout the film one is impressed with the excellent organization of the subject and with the thoroughness and efficiency of the surgical management. The photography is excellent. This production would be suitable to those interested in the organization of public medical facilities. It would be of value to the general practitioner as a demonstration of the present status of surgical management of formidable thoracic conditions and also to the specialist in thoracic surgery as a demonstration of the particular technics in this clinic.

Current Medical Literature

AMERICAN

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Titles marked with an asterisk (*) are abstracted.

American Journal of Clinical Pathology, Baltimore

17:925-992 (Dec.) 1947

Lymphocytic Infiltration and Hemopoiesis in Liver of Tumor Bearing Hamsters. Margaret A. Kelsall and E. D. Crabb.—p. 925.

Effect of Intravenous Administration of Dextran, Macromolecular Carbohydrate, in Animals. M. Goldenberg, R. D. Crane and H. Popper. - P. 939

Verification Antigen for Identification of Pseudosyphilitic Reactions of Serum. H. Hecht.—p. 949.

American Journal of Ophthalmology, Cincinnati

30:1485-1622 (Dec.) 1947

Observations on Pityrosporum Ovale in Seborrheic Blepharitis and Conjunctivitis. J. S. Gots, P. Thygeson and M. Waisman.—p. 1485.

Conjunctivitis with Membrane Formation. M. J. Hogan.—p. 1495.

Studies on Physiology of Eye Using Tracer Substances. R. O. Scholz, D. B. Cowie and W. S. Wilde.—p. 1513.

Sodium-Vapor Lamp and Its Use for Refraction. S. Van Wien. —p. 1527.

Intraepithelial Epithelioma of Cornea and Conjunctiva (Bowen's Disease). B. Esterman, J. Laval and Clara Okrainetz.—p. 1537.

Ocular Changes in Acute Disseminated Lupus Erythematosus: Report of Case With Microscopic Findings. F. C. Cordes and S. D. Aiken. —p. 1541.

*Capillary Fragility and Capillary Permeability in Relation to Retinal Hemorrhage. R. L. Shanno, J. Q. Griffith Jr. and W.O.La Motte Jr.—p. 1556.

*Effect of Visual Training on Existing Myopia. H. R. Hildreth, W. H. Meinberg, B. Milder and others.—p. 1563.

Capillary Fragility and Retinal Hemorrhage.—Shanno and his co-workers think that there is at least a possibility that certain cases of retinal hemorrhage may be due to an alteration in the capillary wall which may be present throughout the body, although obvious lesions may appear only in the retina. To explore this possibility the authors have carried out tests to demonstrate increase in capillary fragility and permeability in the cutaneous capillaries, in patients with retinal hemorrhage. Studies were made on 2 groups of patients, one consisting of 47 subjects with recent retinal hemorrhage who were referred from other dispensaries to a special one set up for this study. The second group consisted of 32 patients with retinal hemorrhage referred as private patients to one of the authors. It was found that a considerable number of patients with retinal hemorrhage have an associated generalized capillary abnormality, as shown by abnormal response to tests for capillary fragility and permeability carried out on the vessels of the skin. The recurrence of retinal hemorrhage during the period of study was usually but not invariably associated with either increased capillary fragility or permeability, as shown by the tests. Rutin therapy was followed by return of capillary fragility and permeability to normal in about half of the dispensary group and in about 70 per cent of the private group; in such subjects further retinal hemorrhage usually failed to develop. In view of the number of cases, the period of follow-up and the diversity of results final conclusions cannot be drawn, but it is at least suggestive that rutin administered in adequate dosage and over a sufficiently long period may be of value in preventing further retinal hemorrhage in that group of patients whose initial hemorrhage was associated with a generalized capillary fault.

Visual Training in Myopia.—Hildreth and others describe research undertaken in an effort to determine the value of visual training as a means of improving the visual acuity in patients with myopia. The procedure required an Arneson squint corrector, a Keystone "tel-eye trainer" with certain Keystone cards and an American Optical Company "Wells-head." The technic was broken into eleven individual steps laid out for a training period of twenty-four days averaging about one hour per day. Of 87 myopic patients 33 were either rejected or the training was incomplete, leaving 54 records for study. Thirty of the 54 patients showed no change in their acuity, while 12 showed a definite improvement, the best results being obtained in the patients with small degrees of myopia. Twelve patients showed a change so slight as to be excluded in the results. The change in the improved group averaged 27 per cent. Eleven of the 12 improved patients were rechecked at an iuterval of fifteen to twenty-three months after completion of training. Five of these retained their improvement, while only 1 had less than pretraining acuity. There was neither change in the refractive error nor significant alteration in the ocular neuromuscular mechanism. It was thought that the improvement probably occurred because of an improved reception due to stimulation of the visual effort. The authors conclude that visual training has a definite but limited value in some myopic patients. The effectiveness of visual training must be increased if it is to be generally applicable. Visual training merits further study by the ophthalmologist.

American Review of Tuberculosis, New York

56:485-610 (Dec.) 1947

Effect of Streptomycin on Pulmonary Tuberculosis: Preliminary Report of Cooperative Study of 223 Patients by Army Navy and Veterans Administration. J. B. Barnwell and others.—p. 485

Streptomycin Therapy in Progressive Pulmonary Tuberculosis: Preliminary Report of Clinical Investigation in 37 Patients. R. O. Canada. —p. 508.

Streptomycin and Bed-Rest in Treatment of Pulmonary Tuberculosis. M. W. Fisher, G. W. Fishburn and J. B. Wallace.—p. 534.

Streptomycin in Treatment of Pulmonary Tuberculosis: Report of 15 Patients. A. Shamaskin, L. C. Morris, E. J. Des Autels and others. —p. 540.

Pulmonary Tuberculosis Treated with Streptomycin: Report of 20 Patients. W. A. Cassidy and E. Dunner.—p. 552.

Streptomycin in Treatment of Pulmonary Tuberculosis: Therapeutic Review of 23 Patients. C. Parnall Jr., B. L. Brock and R. E. Moyer. —p. 565.

Treatment of Pulmonary Tuberculosis with Streptomycin. S. T. Allison and J. M. N. Nilsson.—p. 579.

Streptomycin Therapy with Special Reference to Pulmonary Tuberculosis. N. D. D'Esopo and J. E. Steinhaus.—p. 589.

Streptomycin in Pulmonary Tuberculosis.—Barnwell and others of the Veterans Administration treated 223 patients with moderately and far advanced pulmonary tuberculosis with streptomycin by a uniform regimen in seven Army, Navy and Veterans Administration hospitals. The results of this cooperative venture are described in summary form. Seven additional reports describe in greater detail observations on groups of these patients. The roentgenographic changes in more than half of the cases were viewed by a jury of phthisiologists appointed by the American Trudeau Society. It was the judgment of the jury that little or no change occurred in the productive or fibrocaseous lesions during the hundred and twenty days of treatment but that some degree of clearing occurred in 85 per cent of unstable, exudative lesions, which had been unchanged or progressive in more than two-thirds of the cases for at least sixty days prior to streptomycin therapy. The judgment of the investigators supported that of the jury. This change in the trend of the disease is regarded as evidence that streptomycin can favorably affect pulmonary lesions of this character and that it is superior in this respect to the effects of rest in bed. Extension of lesions occurred in 8 per cent of cases toward the end of treatment in the present series and in 16 per cent during the first to fourth months following its completion. Conversion of results of sputum tests to negative occurred in 40 per cent. In the opinion of the investigators the role of streptomycin in the treatment of pulmonary tuberculosis lies in the partial clearing of exudative lesions, either as an end in itself or as a preliminary to the collapse measures which it often makes possible. The clinical changes during streptomycin therapy were as frequent as the roentgenographic changes and were more impressive in extent. Cough and sputum were almost constantly reduced; fever, when it was present, was similarly affected, and more than 80 per cent of the patients gained an average of 12 pounds (5.4 Kg.) in body weight.

V 1
1948

Laboratory observations established or reaffirmed two gross disadvantages of streptomycin therapy: damage to the vestibular apparatus and the development of resistance by tubercle bacilli, which in all probability makes the long continuation of treatment unprofitable. The possibility of minimizing or avoiding these disadvantages by alterations of the regimen is being pursued.

Annals of Allergy, Minneapolis

5:503-606 (Nov.-Dec.) 1947

*Immunity to Diphtheria Induced by Booster Dose of Diphtheria Toxoid Purified by Absorption and Elution: Based on Study of 55 Allergic Children. M. M. Peshkin and H. G. Rapaport.—p. 503.
Bronchial Asthma in Patients Over Age of 55 Years: Diagnosis and Treatment. A. H. Rowe and A. Rowe Jr.—p. 509.
*Allergens of Mill Dust: Asthma in Millers, Farmers and Others. C. Jimenez-Diaz, C. Lahoz and G. Canto.—p. 519.
Allergy in Glaucoma: Manifestations of Allergy in Three Glaucoma Patients as Determined by Pulse-Diet Method of Coca. C. Berens, L. J. Girard and Edith Cummings.—p. 526.
Anti-Asthmatic Effects of New Synthetic Antispasmodic: Beta-Diethylaminoethyl 9, 10-Dihydroanthracene-9-Carboxylate Hydrochloride. M. M. Hartman.—p. 536.
Methods for Objective Demonstration of Suspected Drug Sensitivity. O. C. Hansen-Pruss and W. E. Leeper Jr.—p. 541.
Chemical Investigations of Giant Ragweed Pollen. G. C. H. Stone, J. Harkavy and G. Brooks.—p. 546.
Application of Tissue Culture Technic in Clinical Evaluation of Bacterial Hypersensitivity. F. A. Nantz and H. Blatt.—p. 554.
Active Sensitization to Pollen. R. P. Wodehouse.—p. 558.
Effect of Drugs in Modifying Response of Asthmatic Subjects to Inhalation of Pollen Extracts as Determined by Vital Capacity Measurements. I. W. Schiller and F. C. Lowell.—p. 564.

Immunity to Diphtheria in Allergic Children.—Peshkin and Rapaport point out that detoxified crude bacterial filtrates and alum-precipitated toxoids are still mainly used in prophylaxis against diphtheria. As a consequence, disturbing systematic reactions occur, especially after the administration of a booster dose of toxoid to older children. Crude toxoid prepared by detoxification of bacterial filtrates with a 40 per cent solution of formaldehyde, in addition to proteins of true exotoxin contains somatic antigens, i. e., soluble substances of proteinic nature that form precipitins with antibacterial serum. Under controlled conditions selective absorption of somatic antigens with magnesium hydroxide can be achieved. This absorption, however, resulted in slight reduction of the total nitrogen content in the toxin. Later methods were developed which made it possible to eliminate more than 90 per cent of the original nitrogen. Purified toxoid was prepared from absorbed toxin by subsequent detoxification with formaldehyde, dialysis, absorption of the toxoid with calcium phosphate and, finally, elution of the purified toxoid. This method yields a highly purified product which contains little nitrogen, is free from bacillary proteins and remains highly antigenic. The authors used these purified diphtherial toxoids in 55 allergic children who had bronchial asthma, hay fever or both. Comparative intradermal tests with a 1:100 dilution of crude yellow diphtherial toxoid and eluted calcium phosphated toxoid showed the latter preparation to give a decidedly lower incidence of positive reactions. The eluted calcium phosphated diphtherial toxoid can be regarded as a preparation pointing to definite progress in the search for diphtherial toxoid capable of lowering the incidence of local, febrile or systemic allergic reactions following its use in allergic children.

Allergens of Mill Dust.—Jimenez-Diaz and his associates show that there exists in cereal dust different elements that can produce sensitization. In order of importance they are fungi, insects, acarina and substances in dust and flour itself. The fungi of greatest importance are rust, smut and Tilletia. They can be found in great quantities in granary dust and in that of milling establishments, owing to their fineness and the ease with which they spread once the covering of the invaded grain has broken. The infected grain, equally with Ustilago and Puccinia, can spread in the air at the time of seed falling, thus acting as causative agents in the sensitization of the population at large. Other fungi, such as Aspergillus and Penicillium, can invade damp flour, but this is a much rarer occurrence. Although little attention has been given to insects as causes of asthma, the authors mention observers who have described sensitization by trichoptera (Caddis fly), ephemerida, Musca domestica and Cimex lectularius. In farmers, in persons who live near granaries or in mill workers investigations carried out by the authors have shown that the sensitizing agent can be coleoptera. Sensitization to flour itself is of most importance among bakers.

Annals of Internal Medicine, Lancaster, Pa.

27:861-1080 (Dec.) 1947. **Partial Index**

Osteoporosis. F. Albright.—p. 861.
Obesity. C. F. Gastineau and E. H. Rynearson.—p. 883.
Poverty of Immunologic Mechanism in Patients with Hodgkin's Disease. I. N. Dubin.—p. 898.
*Efficacy of Maintenance Doses of Digitalis in Preventing Recurrence of Congestive Heart Failure. J. S. LaDue and S. B. Carter.—p. 923
*Streptomycin in Treatment of Tuberculosis in Humans: Pulmonary Tuberculosis. C. Muschenheim, W. McDermott, Susan J. Hadley and others.—p. 989.

Digitalis in Congestive Heart Failure.—LaDue and Carter report on 104 patients with heart disease associated with regular sinus rhythm who had been discharged from Charity Hospital after treatment for congestive heart failure and were followed in the clinic at intervals of from one to four weeks over a period of from six months to two years. At the time the study was begun most of the patients had been taking 0.1 to 0.3 Gm. of folia digitalis for several weeks or months after discharge from the hospital. The data obtained by the authors suggest that vital capacity, circulation time, venous pressure and weight are, at best, crude measurements of cardiac reserve and are less reliable in evaluating this important factor than a careful consideration of the symptoms and signs manifested by a patient with heart disease. This does not detract from the value of these measurements in the study or evaluation of the degree of congestive failure present and of the mechanisms involved in the production and disappearance of cardiac decompensation. Evidence of the efficacy of maintenance doses of folia digitalis in preventing the recurrence of congestive heart failure, although not clearcut, suggests that it may be desirable to keep patients who have had congestive heart failure on maintenance doses of folia digitalis, since the rate of recurrence is twice as great as when the drug is withheld.

Streptomycin in Pulmonary Tuberculosis.—Muschenheim and his associates discuss results observed in 43 patients with pulmonary tuberculosis who were treated with streptomycin for from forty-two to one hundred and twenty days. Of 18 patients whose pulmonary lesions were predominantly exudative, 9 attained satisfactory early remissions during or shortly after the cessation of therapy. Of these, 2 relapsed within six months, requiring collapse therapy, and a third relapsed within twelve months. Another 6 patients showed considerable improvement under streptomycin therapy but fell short of attaining full remission. The suitability of these cases for collapse therapy, however, was appreciably enhanced, and this measure was subsequently undertaken in 5 with apparent success. In 3 patients there was no significant benefit and a short period of symptomatic improvement was followed by resumption of the progressive course. Of another 18 patients with chronic fibrocavernous disease, 4 had satisfactory early responses and 4 more attained favorable results when the antimicrobial therapy was followed by thoracoplasty. In 10 of the 18 cases there was a short period of temporary improvement but no lasting benefit. Strains of tubercle bacilli highly resistant to streptomycin in vitro were obtained from 10 of 11 patients who continued to discharge bacilli during seventy-five to one hundred and twenty days of chemotherapy. The incidence of drug-resistant strains of bacilli was much lower when streptomycin therapy was continued for only forty-two days. When relapse occurred after the appearance of streptomycin-resistant organisms, the infection remained uninfluenced by the further administration of streptomycin.

Bulletin of Johns Hopkins Hospital, Baltimore

81:367-469 (Dec.) 1947.

Nutritional Dermatoses in Rat: XII. Influence of Deficiencies on Extent of Injury and Healing Time of Liquid Mustard Gas Burns. M. Sullivan.—p. 367.
Comparative Efficiency of Single and Multiple Dosage Regimens of Penicillins. C. G. Zubrod.—p. 400.
Diffuse Congenital Cystic Hyperplasia of Stomach Clinically Simulating Carcinoma: Report of Case. H. W. Scott Jr. and T. P. B. Payne.—p. 448.

New York State Journal of Medicine, New York

48:1-112 (Jan. 1) 1948

Subsequen Childbearing of Primigravida Presenting Breech at Term. C. L. Randall and R. W. Baetz.—p. 49.

Puerperal Hemorrhage: Is Present Mortality Rate Unnecessar / High? J. K. Quigley.—p. 55.

Vaginal Hysterectomy. O. N. Eastman.—p. 59.

Is Anal Fistula a Necessary Sequel to Periana Abscess? E. Grane —p. 63.

Practice of Midwives in New York City Helen M. Wallace C. L. Mendelson, Leona Baumgartner and Ruth Rothmayer.—p. 67.

Modification of Incision for Laparotrachelotomy J. T. Wallace and H. J. Merk.—p. 72.

Jaundice and Live Function Tests To What Extent Are They Necessary? B. D. St. John.—p. 75.

Use of Sodium Nicotinate in Treatment of Headache. A. P. Friedman and C. Brenner.—p. 78.

Conservative Treatment of Eclampsia with Emphasis on Stroganoff Method. K. M. Wilson.—p. 79.

Prophylactic Use of Niacin Amide Prevents Anorexia Following Administration of Sulfonamide. L. S. Goldstein.—p. 82.

Niacin Amide to Prevent Anorexia After Sulfonamide Therapy.—Goldstein says that for the past five years he has added to his sulfonamide prescriptions 50 mg. of nicotinamide (niacinamide), and he has found that this will prevent the anorexia that usually follows medication with sulfonamide drugs.

Public Health Reports, Washington, D. C

62:1785-1812 (Dec. 26) 1947

Pteroylglutamic Acid ("Folic Acid"), Liver Extract, and Amino Acids in Treatment of Granulocytopenia in Rats. F. S. Daft.—p. 1785.

Serum Protection Test in Tularemic Infections in White Rats. C. L. Larson.—p. 1793.

63:1-40 (Jan. 2) 1948

Tuberculosis Mortality in Major Cities. United States, 1945 Sara A. Lewis and R. V. Kasius.—p. 3.

63:41-68 (Jan. 9) 1948

Preliminary Report Concerning DDT Dusting and Murine Typhus Fever in Nine Southeastern States. J. S. Wiley.—p. 41.

Some Factors Influencing Mouse Potency Test for Rabies Vaccine K. Habel and J. T. Wright.—p. 44.

63:69-96 (Jan. 16) 1948

Estimate of Incidence of Chronic Disease. P. S. Lawrence.—p. 69.

Surgery, St. Louis

22:889-1052 (Dec.) 1947

*Streptomycin in Surgical Infections: IV. Peritonitis. E. J. Pulaski, S. F. Seeley and C. S. Matthews.—p. 889.

Studies in Experimental Frostbite: I. Effect of Heparin in Preventing Gangrene. H. B. Schumacker Jr., Beverly H. White, E. L. Wrenn Jr. and others.—p. 900.

Use of Anticoagulants in Surgery of Aneurysms and Arteriovenous Fistulas, with Particular Reference to Dicumarol. H. B. Shumacker Jr., D. I. Abramson and H. H. Lampert.—p. 910.

*Pulmonary Arteriovenous Aneurysm, a New Surgical Disease W. L. Watson.—p. 919

Peripheral Arteriography. L. J. Kleinsasser.—p. 930.

Chronic Eventrations and Large Hernias. Preoperative Treatment by Progressive Pneumoperitoneum—Original Procedure. I. G. Moreno. —p. 945.

Cushing's Syndrome Associated with Fuchsinophilic Staining Reaction in Adrenal. A. H. Pedersen and T. J. Kenyon.—p. 954.

Radical Pancreatoduodenectomy with Resection of Patent Portal Vein. Experimental Study. P. W. Schafer and J. S. Kozy.—p. 959.

Method of Cranioplasty Using Ready-Made Acrylic Cranioprostheses. H. J. MacKay.—p. 965.

Condylar Growth and Mandibular Deformities. M. B. Engel and A. G. Brodie.—p. 976.

Zippered Elastic Stockings. H. D. Cogswell.—p. 993.

Streptomycin in Surgical Infections.—Pulaski and his associates say that the sulfonamide drugs, penicillin and streptomycin are by no means solely responsible for the reduced mortality in peritonitis. The management of peritonitis now includes, in addition to chemotherapy and antibiotic therapy, intestinal decompression, correction of fluid and electrolyte balance and of protein depletion and measures to prevent or treat thrombophlebitis and phlebothrombosis with threatening pulmonary infarction and embolism. The 63 cases of peritonitis which are reported form a heterogeneous group in respect to etiologic basis, management, dosage and duration of therapy. All the patients were desperately ill, but they were predominantly young men in good health. Of the 5 deaths, 3 were due to nonbacterial causes. In the other 2 cases streptomycin was added to other forms of therapy when the patients were already moribund. Eighteen of the 58 patients who recovered were treated only with streptomycin; the remaining 40 patients were treated with streptomycin and penicillin, supplemented in 10 cases by sulfadiazine. Immediate dramatic results were seldom observed following the administration of streptomycin, whether it was used alone or in combination with penicillin, although in both spreading and localized peritonitis recovery was thought to be more smooth and rapid when the drugs were used in combination. Resolution of peritoneal suppuration in the streptomycin series was of approximately the same pattern as is seen in patients receiving penicillin in excess of 800,000 units. Results were generally less striking when streptomycin was employed in infections which had already localized. The dosage of streptomycin varied between 1 and 4 Gm. per day, administered by the intramuscular route in divided doses at intervals of three or four hours. In a few instances streptomycin in amounts up to 0.5 Gm. was introduced into the peritoneal cavity at the time of operation. Consistently beneficial effects could never be attributed to streptomycin when the dosage was 2 Gm. per day or less. Harmful effects were not observed in consequence of daily dosages of 3 Gm. per day for ten to fourteen days, although minor untoward reactions occurred in approximately 20 per cent of the cases. Patients who received 3 Gm. per day of streptomycin alone or 2.5 Gm. in combination with an average of 480,000 units of penicillin had the most satisfactory postoperative convalescence. Streptomycin is not a panacea, yet it has a valuable place in the treatment of peritonitis

Pulmonary Arteriovenous Aneurysm.—Watson states that the medical literature contains reports of only 10 cases of congenital or nontraumatic pulmonary arteriovenous aneurysm. The lesions have been reported as cavernous hemangioma of lung, multiple pulmonary hemangiomas and arteriovenous fistula of lung. As the gross anatomic structure consists of a lobulated, thin-walled, branching, blood-filled pulsating pulmonary sac made up of both an arterial and a venous component, it seems more logical to call these lesions pulmonary arteriovenous aneurysms in order to distinguish them from benign hemangiomas of the lung, metastatic pulmonary hemangiomas or hemangioendotheliomas of the lung. A pulmonary arteriovenous aneurysm produces a shunt whereby a considerable amount of blood passes from the arterial to the venous circulations of the pulmonary circuit without passing through the alveoli of the lung to be oxygenated. This results in a low oxygen saturation of the arterial blood. A patient so afflicted is in danger of hemorrhage which may prove fatal, of cerebral thrombosis with epileptiform seizures due to the slowed circulation and of increased volume in red blood cells. Coronary artery thrombosis is also known to occur. A mild degree of invalidism necessitating curtailment of activities is usual. Six patients have been cured by surgical measures. The histories of 2 of these are reported. Surgical measures varying from pneumonectomy, lobectomy and multiple local excisions to ligation of the offending, or "feeder," artery have been carried out, and there have been no postoperative fatalities. The untreated or medically managed patients have not improved or have died. Although pulmonary arteriovenous aneurysm is apparently a congenital lesion, symptoms may not appear until the age of 14 or 16 years. In 1 of the author's cases, the patient had reached the age of 27 and the lesion was causing no symptoms and was discovered by chance radiography. The diagnosis is suggested by a syndrome characterized by cyanosis, clubbing of the fingers and toes, secondary polycythemia and symptoms of anoxemia, usually in a young patient with an obscure pulmonary tumor and a normal heart. A bruit may be heard over the tumor. A gradual, expansive enlargement and thinning out of the walls of the vascular tumor probably takes place slowly over a period of years, and spontaneous hemorrhage occurs, as in case 2 of this report, when some slight overexertion increases the intrapulmonary pressure enough to cause a break.

Wisconsin Medical Journal, Madison

46:1189-1308 (Dec.) 1947.

Tuberculosis in the Older Age Group. C. D. Boyd.—p. 1203.

Hospital Postgraduate Education. O. O. Meyer.—p. 1205.

Visual Education for Laity in Hospital Public Rooms. A. S. Jackson. —p. 1207.

V 13
1948

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted. Single case reports and trials of new drugs are usually omitted.

Practitioner, London

159:427-498 (Dec.) 1947

Present Status of Tonsillectomy. W. A. Mill.—p. 427.
Some Unusual Conditions of Throat. V. E. Negus.—p. 436.
Present Status of Penicillin and Sulfonamides in Infections of Throat. W. I. Daggett.—p. 442.
Problem of Diphtheria Carrier. E. H. R. Harries.—p. 446.
Throat in Relation to Singing and Public Speaking. R. S. Stevenson. —p. 452.
Atomic Physics in Medicine. S. Rowlands.—p. 459.
Fits in Children. A. D. Bell.—p. 463.
Treatment of Psychologic Conditions in General Practice. A. Guirdham. —p. 468.
Post-Anesthetic Vomiting and Chest Complications. H. P. Price.—p. 474.

Thorax, London

2:169-223 (Dec.) 1947

Giant Bullous Cysts of Lung. P. R. Allison.—p. 169.
Mediastinal Cysts of Bronchial Origin. P. R. Allison.—p. 176.
*Treatment of Bronchopulmonary Suppuration by Local Injection of Penicillin. Report of 63 cases. H. Métras and J. Lieutier.—p. 196.
Complete Occlusion of Superior Vena Cava with Chronic Mediastinitis in Case of Generalized Actinomycosis. J. P. D. Mounsey.—p. 203.
Radiotherapy in Cancer of Thoracic Esophagus. J. A. C. Fleming. —p. 206.
Results of Thoracoplasty in Pulmonary Tuberculosis. T. H. Sellors. —p. 216

Local Penicillin in Bronchopulmonary Suppurations.—Métras and Lieutier say that after using Thomson's catheter for bronchography, one of them designed a set of special radiopaque rubber catheters which allow the injection of radiopaque substances not only into a lobe but even into separate and selected bronchopulmonary segments. After they had used the special catheters for bronchography, they used them also to inject penicillin directly into a pulmonary abscess by way of the tracheobronchial tree. The tracheobronchial tree is first anesthetized with a 1 per cent solution of pontocaine hydrochloride and the catheter is introduced into the trachea. The patient is placed behind the fluorescent screen, then the catheter is directed toward the bronchus of the diseased segment and placed as near as possible to the bronchus of drainage. The patient is then placed in such a position that the end of the sound and the affected segment are vertically downward. The patient is arranged comfortably in this position, and 100,000 units of penicillin in 5 to 10 cc. of isotonic sodium chloride solution are injected slowly; the patient remains in the same position for thirty minutes. The injection should be repeated every two days. The average number of injections needed is eight. For the bronchi of the middle and lower lobes the ordinary bent catheter is adequate; for the bronchi of the upper lobes it is necessary to use catheters with a double turn if an adequate injection is to be achieved. Sixty-three patients have been treated. The results show that local instillation of penicillin is worth while either because it provides an easy and quick method of improving the condition of the patient before operation or because it can cure with little disturbance and few manipulations many patients who would otherwise be judged hopeless. In the series of 63 cases, 75 per cent recovered and 17 per cent have undergone an operation for extirpation of the disease.

Sang, Paris

18:453-520 (No. 8) 1947. **Partial Index**

Atypical Aleukemic Lymphadenia Associated with Eosinophilia, with Reference to Certain Modes of Development (Involution or Transition to Lymphosarcomatosis). P. Ravault and P. Guinet.—p. 453.
*Agranulocytosis of Schultz's Disease Type Intensive Penicillin Treatment Combined with Injections of Pentose Nucleotide and Liver Extracts; Recovery. B. Muller, P. Bouquin and A. Meyrieux.—p. 493
*Ascorbemia in Pulmonary Tuberculosis. Lafontaine.—p. 499.

Penicillin in Agranulocytosis.—Muller and his co-workers report the occurrence of agranulocytosis of the type of Schultz's disease in a man aged 46 with sore throat who presented symptoms of severe infection. His general condition was grave; there was pronounced asthenia and rise of temperature to 104 F (40 C.). Nondiphtheric false membrane covered pharyngolaryngeal necrotic ulcers. Icterus occurred in the absence of hypertrophy of the hematopoietic organs and the liver. Leukopenia (1,250 white blood corpuscles) associated with a nearly total disappearance of granulocytes (5 per cent) was demonstrated on hematologic examination. Sulfathiazole and antidiphtheritic serum were ineffective. Penicillin treatment was instituted with doses of 480.000 to 800,000 units per day by intramuscular route and was continued for twenty-five days; the total dose amounted to 12,970,000 units. This was combined with injections of pentose nucleotide and liver extracts. Following the start of the penicillin treatment, there was a drop in the temperature, which was gradually restored to normal. The general condition improved considerably. Regeneration of the blood progressed rapidly, thus demonstrating that the bone marrow was damaged but not destroyed anatomically. It may also explain the late occurrence of a secondary abscess of the submaxillary glands associated with polynucleosis warranting a favorable prognosis. Progressive improvement has continued for several months, suggesting a definite recovery with little risk of recurrence.

Ascorbemia in Pulmonary Tuberculosis.—Lafontaine determined the excretion of ascorbic acid in the urine, the level of ascorbic acid in the blood and the excretion of ascorbic acid in the urine after the administration of massive test doses of ascorbic acid (vitamin C) in 172 patients with pulmonary tuberculosis and in 20 healthy persons who lived under the same conditions, were placed on the same diet and were given the same amount of rest as the patients with tuberculosis. Results demonstrated a disturbance of the metabolism of ascorbic acid in the tuberculous patients; it was manifested by a decrease of the excretion of ascorbic acid in the urine, by a diminished level of the ascorbemia and by an increase in the retention of the agent following the administration of excessive test doses of ascorbic acid. Graphic records of the ascorbemia after the intravenous injection of ascorbic acid showed that the disturbance of metabolism is one of increased want rather than one of absorption or of excretion. The increase in the necessary amount persists in spite of the administration of massive doses of ascorbic acid. To some extent the disorder may be attributed to the tuberculous condition. The disturbance of excessive consumption of ascorbic acid is the more pronounced the severer the patient's condition, with the exclusion of other phenomena which may have an effect on the metabolism of ascorbic acid. There was no evidence of any therapeutic effect of ascorbic acid on the pulmonary tuberculosis or even on the hemoptysis.

Nordisk Medicin, Gothenburg

36:2259-2306 (Nov. 14) 1947. **Partial Index**

Digitoxin—Cardiac Glycoside in Light of Recent Investigations. S. Wiedling.—p. 2259.
Care of War Victims in Finland. J. Heinonen.—p. 2264.

Hospitalstidende

Mucocele, in Appendix with Pseudomyxoma Peritonei. F. Bergan. —p. 2272.

Hygiea

*Etiology of Toxemia of Pregnancy. A. Edlén, B. Knutsson and K. Palmstierna.—p. 2281.
Psoriasis Provoked by Acute Polyarthritis. O. Ljung.—p. 2285.

Svenska Läkaresällskapets Förhandlingar

Dental Caries and Acid-Forming Bacteria. G. Bremer and P. Varenius. —p. 2289.
Principles for Treatment of Malignant Tumors. J. Hellström.—p. 2296.

Etiology of Toxemia of Pregnancy.—Edlén and his associates studied the relation between toxemia and blood groups in mother, father and child in 129 recent pregnancies. In the 31 cases in which the father had group O blood toxemia occurred in only 1 case; in the 59 in which both partners belonged to the same blood group and in the 7 in which the mother's blood group was AB it did not occur. These pregnancies are regarded as homospecific, other pregnancies as heterospecific. Toxemia of pregnancy occurred in 7 of 10 cases of heterospecific pregnancy in primiparas and in 4 of 22 cases in multiparas. The father's blood group, unless the mother belongs to the AB group, plays a decisive part in the origin of toxemia. The occurrence of toxemia probably depends on two factors, the hypophysis-thyroid hyperfunction normal in all pregnancies and a foreign factor; this latter factor, the authors maintain, is heterospecific protein transmitted from the father. Toxemia of pregnancy is thus regarded as an allergic reaction of the mother's organism to foreign protein. The results of attempts at prophylactic desensitization of the mother in heterospecific pregnancies by intracutaneous injection of the father's serum will be published later.

Industrial Medicine, Chicago

16:519-566 (Nov.) 1947. **Partial Index**

Orienting the New Employee in Services of Industrial Health Department. Jean S. Felton.—p. 519.
*Causalgia. P. Pernworth.—p. 525.

Causalgia.—Pernworth says that industrial surgeons are occasionally confronted with the apparent paradox of minor trauma producing severe subjective complaints. When the patient's symptoms greatly exceed the objective observations it is usual to give at least tacit consideration to some element of malingering. However, there is one well established syndrome which may follow insignificant injury. To this condition of autonomic derangement have been applied the terms reflex sympathetic dystrophy, causalgia or Weir-Mitchell's syndrome. When bony changes are prominent the phenomenon is termed Sudeck's atrophy. Whenever sympathetic dystrophy is suspected, a block of the autonomic nerve supply to the affected area should be induced with procaine hydrochloride. Response to anesthesia of the involved sympathetic ganglion is a reliable diagnostic criterion of this condition. The author illustrates this by a case report. He concludes that causalgia should be considered as an etiologic factor in all chronically painful limbs that show vasomotor changes.

Journal of Investigative Dermatology, Baltimore

9:219-276 (Nov.) 1947. **Partial Index**

New Factors in Adhesive Formulas Which Lessen Irritation. R. E. Humphries.—p. 219.
Studies of Sweating: I. Preliminary Report with Particular Emphasis on Sweat Retention Syndrome. M. B. Sulzberger, F. Herrmann and F. G. Zak.—p. 221.
New Series of Fungicidal Fatty Acid Esters. E. S. Bereston.—p. 243.
Specificity of Skin Tests in Deep Fungus Infections. L. Katzenstein. —p. 249.

Medicine, Baltimore

26:333-498 (Dec.) 1947

Filariasis in American Armed Forces in World War II. W. B. Wartman.—p. 333.
Nervous System in Tropical Disease: Clinical Review W. S. Chalgren and A. B. Baker.—p. 395.
*Clinical Patterns of Undifferentiated and Other Acute Respiratory Diseases in Army Recruits. J. H. Dingle, T. J. Abernethy G. F. Badger and others.—p. 441.
*Bacteriologic Findings in Undifferentiated and Other Acute Respiratory Diseases. J. H. Dingle, T. J. Abernethy G. F Badger and others. —p. 465.

Clinical Patterns of Acute Respiratory Diseases.—Dingle and his co-workers present a classification of acute respiratory disease as it occurred among recruits in the army during three years of observation. From 75 to 90 per cent of all respiratory admissions to the hospital were due to a syndrome of undifferentiated acute respiratory disease. The average clinical pattern of this syndrome did not change in three separate studies in different seasons. The cases were characterized by a short febrile course and presented a combination of general constitutional symptoms with a prominence of symptoms suggesting involvement of the tracheobronchial tree. Symptoms of nasal involvement were less common. It was a disease without characteristic physical observations and with a normal leukocyte count. Its etiology was unknown. There was no suggestion of a bacterial cause and much to suggest a virus etiology. Exudative tonsillitis and pharyngitis was responsible for 10 to 15 per cent of respiratory admissions. In half of the cases, beta hemolytic streptococci were not found. These cases not due to streptococci had a rather characteristic pattern of symptoms and of physical signs in the throat. They were not dissimilar from cases of undifferentiated acute respiratory disease, of which they may be a variant. In the remainder of the cases of exudative tonsillitis and pharyngitis the throat harbored beta hemolytic streptococci. In some of these streptococcic antibodies developed. The latter cases conformed to a pattern of symptoms and physical signs which was distinctive and set them apart from all the other groups. The remainder were cases in which diagnostic antibody responses did not develop. Some were probably true streptococcic infections, but most resembled nonstreptococcic exudative tonsillitis and pharyngitis superimposed on a streptococcic carrier state. Only a small part of the total admissions for acute respiratory disease was made up of primary atypical and bacterial pneumonias and a miscellaneous group of other respiratory infections.

Bacteriologic Data in Acute Respiratory Diseases.—Dingle and his co-workers agree with Bloomfield that the most efficient method of studying the relationship of minor respiratory disease and the bacterial flora of the respiratory tract is by taking serial cultures before, during and after colds, employing the same subjects repeatedly over a period of time. Human volunteers were subjected to inoculation with infectious material, and bacteriologic observations were made at two day intervals throughout prolonged preinoculation and postinoculation periods. No changes in flora were noted during illness which were greater than those seen in the same persons before illness or in other persons not inoculated. In a similar manner serial throat cultures were obtained from several platoons of army recruits. Evidence was not obtained that changes in bacterial flora occurred in relation to the onset of colds. In both studies considerable variation was observed in the carrier rates of several organisms grown from these cultures These variations were not related to the development or to the general prevalence of minor respiratory illness. Throat cultures of men hospitalized for undifferentiated acute respiratory disease and influenza revealed no differences which could be associated with their illnesses, in contrast to results in those with infections due to beta hemolytic streptococci.

New England Journal of Medicine, Boston

237:969-1004 (Dec. 25) 1947

*Diarrhea of the Newborn: Its Causes and Prevention S. H. Clifford. —p. 969.
Unusual Case of Acute Infective Polyneuritis with Visceral Lesions. F. Parker Jr. and R. D. Adams.—p 976.
Emphysematous Gastritis. C. E. Welch and C. M. Jones.—p. 983.
What Industry Thinks About Massachusetts Medical Society's Program of Medical Care for People of Massachusetts J. Hunt.—p. 986.
Nasal Carrier of Beta-Hemolytic Streptococci. H. M. Lemon.—p. 988.
Acute Oophoritis and Perioophoritis.—p. 995.
Rheumatic Heart Disease, with Mitral Stenosis and Insufficiency. Mural Thrombus of Left Auricle. Cerebral Embolus of Left Middle Cerebral Artery.—p. 997.

Diarrhea of the Newborn.—Clifford shows that the emergence of epidemic diarrhea in the newborn as a public health problem coincides with the transfer of childbirth from the home to the hospital. Hospitals have been unprepared for this migration, and crowding infants into nurseries, in addition to the shortage of personnel, has produced conditions favorable for the spread of infection. There is a national need for more beds for obstetric patients and for more nurseries, each to be limited to 8 to 12 newborn infants. In five epidemics a specific virus etiology has been proved. This virus is probably the cause of other outbreaks, but many epidemics of diarrhea in the newborn have been traced to a variety of pathogenic organisms that could only reach the infant by the fecal-oral route. In a large percentage of these outbreaks investigators have found evidence of gross breaks in nursery technic. The first obligation is to block all routes by which the infant can acquire bacterial infection in the nursery through a strict application of known nursery and formula-room technics.

New Jersey Medical Society Journal, Trenton

44:479-532 (Dec.) 1947 **Partial Index**

Reconstructive Surgery of Extremities. J. J. Flanagan.—p. 482.
Primary Attack of Benign Tertian Malaria Fourteen Months After Cessation of Suppressive Therapy. I. L. Sperling.—p. 487.
Diagnosis and Management of Pelvic Endometriosis. F. L. Payne. —p. 496.
*Relationship of Occupational Strain to Rectal Conditions. S. Zager. —p. 501
Headache: Impressions of an Ophthalmologist. F. D. Carroll.—p. 503.

Occupational Strain and Rectal Conditions.—Zager says that some standard textbooks, specifically Bacon, mention as predisposing to hemorrhoids "severe muscular strain such as lifting" and increased intra-abdominal pressure such as "straining from coughing, sneezing and vomiting." Authorities considered procidentia of the rectum a form of "sliding hernia," and for this reason its parallel to the compensable situation of inguinal hernia is not too far fetched. The author relates histories of 3 workers in whom rectal symptoms appeared after heavy lifting or pulling and who were granted compensation. He thinks that preemployment physical examination should be more carefully performed to rule out the possibility of preexisting disease of the rectum. The Workmen's Compensation Act pays for aggravation as well as for direct cause.

V 13
1948

Book Notices

Gastroenterology in General Practice. By Louis Peiner, M.D., Associate Attending Physician Greenpoint Hospital, Brooklyn. With the collaboration of Louis A. Reid, M.D., Attending Roentgenologist, Beth Moses Hospital, Brooklyn and contributions from Alexander Lewitan, M.D., Consulting Roentgenologist, Norwegian Public Health Service, New York, Samuel Waldman, M.D., Associate Attending Physician, Greenpoint Hospital, Brooklyn, and Siegfried W. Westing, M.D., Roentgenologist, Brooklyn Cancer Institute, Brooklyn. Fabrikoid. Price, $7.50. Pp. 285, with 109 illustrations. Charles C Thomas, 301-327 E. Lawrence Ave., Springfield, Ill., 1946.

The aim of the author as stated in the preface is to make this "an every day hand-book rather than a complete reference work." While he succeeds in accomplishing this purpose there is probably little need for such an elementary book in the library of the general practitioner. Any standard textbook of general medicine will supply all that is found in this book plus fairly complete descriptions of the other common diseases encountered in medicine. The chapters on psychosomatic problems are well written and will be of value to the practitioner.

Walk with a Separate Pride. By Sheila Alexander. Cloth., Price, $2.50. Pp. 158. The Itasca Press, a division of The Webb Publishing Co. 55 E. Tenth St., St. Paul 2, 1947.

The author of this book was seven months pregnant when her husband left for the wars. Her book is a psychologic document, imaginative, poetic and sensitive. As fiction it will appeal to few readers. As a contribution to the stream of consciousness, it will be of special interest to the psychologists and the psychiatrists.

The American Sanatorium Association: A Brief Historical Sketch. By Lewis J. Moorman, M.D. Historical Series Number 3. Paper. Pp. 72, with portraits. National Tuberculosis Association, 1790 Broadway, New York 19, 1947.

This booklet presents a historical account of the development and organization of the American Sanatorium Association, now known as the American Trudeau Society. Included is a record of its meetings and transactions since the establishment in 1905, giving not only a list of committees and their functions, papers, discussions and other activities, but also the names of physicians who have taken a prominent part in the work of the association. As these events and activities unfold, the reader will gain a clearer understanding of the progress that has been made in the sanatorium field since the turn of the century. The booklet will be of interest to physicians associated with sanatorium services as well as to others who are concerned in the treatment and care of those with tuberculosis.

Office Treatment of the Eye. By Elias Selinger, M.D., Attending Ophthalmologist, Mount Sinai, Cook County and Michael Reese Hospitals, Chicago. Cloth. Price $7.75. Pp. 542, with 67 illustrations. Year Book Publishers, Inc., 304 S. Dearborn St., Chicago 4, 1947.

Since probably 90 per cent of most ophthalmic practice is office practice, this textbook contains much the same material that is to be found in good textbooks of ophthalmology except for major surgical problems. The important difference is in the approach to the subject and the difference in stress on various phases. There is little anatomy and not much that could be considered primarily instructional at the level of the undergraduate medical student. It is assumed that the reader is grounded in the fundamentals though the more abstruse problems, such as those concerning the handling of the extraocular muscular abnormalities, are considered in great detail. The book tends to be a treatise on therapy and is up to date along these lines. The writer is rather conservative in his advice, the book being free from radical suggestions. The average ophthalmologist will probably not find much that is new to him but will enjoy the easy readability and sound advice. The illustrations, printing and format are acceptable. The book can scarcely be considered a "must" for the practicing ophthalmologist but rather a pleasing addition to his ophthalmic library.

Studies in Genius. By Walter G. Bowerman. Cloth. Price, $4.75. Pp. 343. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1947.

After defining genius, the author analyzes the list of eminent Americans as to their birthplace, heredity, marriage, height and weight, cause of death and similar factors. Among 973 eminent Americans he includes twenty-four physicians, and as to the genius of some of them there might be considerable doubt. The book presents some interesting speculations but little that can be practically helpful in selecting and encouraging genius.

The Science Digest Reader: A Selection of Outstanding Articles Published in Science Digest During the Past Ten Years. Cloth. Price, $3. Pp. 310. Windsor Press, 200 E. Ontario St., Chicago 11, 1947.

From the periodical called *Science Digest* the editors have selected a number of articles published during the past ten years. A few are in the field of medicine, for example, "Foolish Fancies About Your Health," "The Gifted Child," "Your Stomach Is Really a Gland" and "Childbirth Without Pain." Several of the articles are republished from *Hygeia*.

How Our Minds Work. By C. E. M. Joad. Cloth. Price, $2.75. Pp. 116. The Philosophical Library, Inc., 15 E. 40th St., New York 16, [n. d.].

Innumerable books have been published recently trying to explain modern psychology to the average reader. Influence of the mind on the body is now generally accepted, and psychosomatic medicine has a well recognized position in medical circles. Dr. Joad's book is an exceedingly brief analysis of current points of view and quite inadequate in simplifying for the general reader the controversies that prevail in modern psychology and psychiatry. He concludes by insisting that the unconscious is not nearly as important as the psychoanalysts insist, but he recognizes that some extraordinary results have been achieved by psychoanalytic methods.

Reading and Visual Fatigue. By Leonard Carmichael, Ph.D., President, Tufts College, and Director, Tufts Research Laboratory of Sensory Psychology and Physiology, Medford, Mass., and Walter F. Dearborn, M.D., Ph.D., Director, Psycho-Educational Clinic, and Professor of Education, Harvard University, Cambridge, Mass. Cloth. Price, $5. Pp. 483, with 103 illustrations. Houghton Mifflin Co., 2 Park St., Boston 7, 1947.

A committee of well known scientists and educators, known as the Committee on Scientific Aids to Learning, financed a series of investigations of reading. These began in 1940 at Harvard University and Tufts College and were continued by one of the investigators at the University of Rochester. Special types of apparatus were developed for recording eye movements.

Modern industrial and educational processes place a tremendous burden on vision. Some physicians have even credited continuous, fatigue of the eyes with being the foundation of the "neurotic tendency" of our times. After a definition of visual fatigue the authors present their consideration of the factors involved in reading and the relation of these factors to fatigue. The technic of the experiments is described in detail, followed by a discussion and interpretation of the results. An excellent summary and conclusions provide the general reader with the true significance of the study.

Apparently one may assume that the total visual mechanism is able to function approximately as effectively at the end of a long period of continuous activity—as much as six hours—as at the onset of that activity. An analogy is made with the heart. The heart muscle can recuperate in the short time intervals between its contractions. When needed, the heart can rise to new levels of activity. Proper athletic training assists in conditioning the heart and the circulation for the new effort. The factors of safety in the construction of the eye are great, and its muscles are larger and stronger than necessary for most of the movements that the eye may make. This leads to the conclusion that the long periods of study required of high school

and college students are not injurious to their eyes. The final conclusion of the authors is also important. The first index of fatigue comes in alterations of the general attitudes and general feelings of the person concerned rather than in a breakdown of the sensory neuromuscular mechanism which actually performs the task.

The Master Hand: A Study of the Origin and Meaning of Right and Left Sidedness and its Relation to Personality and Language. By Abram Blau, M.Sc., M.D., C.M., Assistant Clinical Professor of Psychiatry, New York University College of Medicine, New York. Research Monographs No. 5. American Orthopsychiatric Association, Inc. Cloth. Price, $4.50. Pp. 206, with 13 illustrations. The American Orthopsychiatric Association, Inc., 1790 Broadway, New York 19, 1948.

The subject here considered has attracted much scientific attention in recent years. Some of the author's conclusions may still be debatable. He does not find that preferred laterality or the preference for either the right hand or the left hand is inherited. He considers it a complicated developmental psychologic trait. "Evidence indicates that preferred laterality is manifested not only between hands but between eyes, legs and other human functions. Some persons prefer to walk on one side of the street rather than the other. Few ambidextrous persons indeed are equally competent on both sides. Animals do not show preferred laterality as do human beings. In human beings the preference for the right side is a cultural and social convention. An infant does not have any preference for one side or another, but our environment is built on righthandedness and preference for one side or another usually becomes apparent at about 9 months of age. Lefthandedness represents a failure to learn righthandedness, according to the authorities. Any physical defect in the right hand enforces use of the left. Left-handed parents are unconsciously models for lefthanded children. The author believes that the commonest type of lefthandedness is due to emotional contrariness in early childhood. Cerebral dominance is related to handedness, so that persons are left-brained because they are righthanded. The author recommends that children be encouraged in their early years to adopt right-handedness because thus the child will be better equipped to live in a righthanded world. He does not believe that there is any danger in restraining or retraining children in handedness. The most he finds that is required is careful and sympathetic training in the use of the other hand with proper directional orientation.

Your Teeth: And How to Keep Them. By Jerome J. Miller, D.D.S. With an Introduction by C. Raymond Wells, D.D.S., Sc.D., Captain, Dental Corps, U. S. Naval Reserve. Cloth. Price, $3. Pp. 232, with 44 illustrations. Lantern Press, Inc., 257 Fourth Ave., New York 10, 1947.

This volume, written by a practicing dentist and teacher of dentistry, attempts to present intelligibly answers to questions about teeth and their care to the lay reader. While the book is intended primarily for the nonmedical person, it may have real usefulness to the physician in interpreting such material to his patients.

Facts about the structure and growth of teeth are introduced in relation to proper care and as a background for good oral hygiene. Common dental problems that arise at various age levels are discussed with special attention to the care of children's teeth. The author refutes the general belief that there are "hard and soft teeth" and makes a strong case against "fear of dental pain" in view of local and general anesthetics, drugs to calm the highly nervous person and advances in dental technic. Restorative dental treatment and appliances are dealt with at some length, with skilled dental service rather than the appliance receiving major emphasis. Simple cleansing of the teeth together with regular dental care are stressed as important principles of dental health.

The book is written in understandable language, and is illustrated with line drawings where graphic clarification seems valuable. The author has honestly labeled theories as such, has been careful in interpreting facts and has not hesitated to admit limitations of present knowledge.

Overcoming Stammering. By Charles Pellman. With a foreword by Dr. Frederick Martin. Cloth. Price, $3. Pp. 160. The Beechhurst Press, Inc., 296 Broadway, New York 7, 1947.

This book attempts to present a practical system for the treatment of the stammering child. The terms stammering and stuttering are considered synonymously in the text. The author, a practicing speech correctionist, advocates reconditioning the speech reflexes, contending that stammering must be overcome by developing the faculty of speech itself. He takes issue with those who look on stammering as the symptom of an inferior nervous constitution and with those who seek to achieve correction solely through public speaking, breath control or word substitution and the like.

The method involves learning speech over again, in an objective way, following essentially the same steps by which a child learns to talk. Fundamental and auxiliary drills are employed, and a partial silence to allow for the setting of new speech responses is a part of the procedure. Tongue, facial and general physical exercises are used to break down muscular rigidity. A great deal of attention is given to dispelling speech consciousness and the fears which beset the stammerer. Emphasis is placed not only on eliminating the defect but also on aiding the child to become a proficient speaker. A portion of the book is devoted to suggestions as to how the intelligent parent can help in the process.

The theories presented, stressing correction primarily through reconditioning speech patterns and improving mental hygiene, should be of interest to parents, teachers and physicians concerned with this problem.

Digitalis and Other Cardiotonic Drugs. By Eli Rodin Movitt, M.D., Captain, Medical Corps, Army of the United States. Cloth. Price, $5.75. Pp. 204, with 15 illustrations. New York: Oxford University Press, 1946.

An excellent summary of the present day information on digitalis and related compounds is given in this small and readable book. The various components of digitalis are reviewed in detail, starting with a brief historical account of the fractions the structural chemistry, specific pharmacologic properties and clinical experiences. A number of diagrams throughout the book clearly illustrate some of the aspects of the digitalis fractions that are confusing to the average practitioner. Basic chemical reactions and structural formulas afford the reader an opportunity to see the latest developments in the field of glycosides and materially clarify parts of the text that would otherwise be of benefit only to research workers in the field of cardiology. A number of graphs demonstrate pharmacologic action in terms of energy liberation, work performance, efficiency of operation, pulse, heart volume and absorption and elimination of the various drugs. It is to be regretted that there are few electrocardiograms shown on pages 80, 99 and 105 and those few rather poorly printed.

The discussion on strophanthus, squill, thevetin and other drugs of plant and animal origin is accurate and well written. A number of minor errors unfortunately appear in the book, as venus pressure on page 9. Some will question the unqualified statement on page 25: "One should remember that in acute myocardial infarction the displacement of the RS-T segment takes place in the opposite direction (above the iso-electric line) from that observed in digitalis effect." On the whole, it is an excellent book on digitalis and allied substances that should be of real value to the general practitioner and the internist. An excellent review of the literature, a well prepared bibliography and a good index enhance the usefulness of the book, which is basically a fair statement of present knowledge of the subject in easily readable and enjoyable style.

V 13
1948

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS BUT THESE WILL BE OMITTED ON REQUEST.

DIPHTHERIA VIRULENCE

To the Editor:—We frequently hear of "diphtheria carriers" held for weeks or months of observation on account of suspicious diphtheroids as visualized on smear by some technician. In many of these cases the faucial lesion or membrane and/or the clinical course or therapeutic response are not especially typical of infection due to Corynebacterium diphtheriae. I would appreciate answers to the following questions: 1. Does a microscopic smear ever justify a positive differential diagnosis between a true virulent diphtheria and a nontoxic diphtheroid? 2. Can a positive statement as to the degree of virulence be justified from rough or smooth appearance of the culture? 3. Can the same organism, found to be nontoxic by guinea pig inoculation on one occasion, be capable of changing its virulence after repeated cultures or after repeated animal or human passage? 4. Should inoculation of toxin for virulence in guinea pigs be mandatory in the study of all cases of diphtheroid? 5. What is the latest thought regarding the value of the tellurite technic relative to virulence of diphtheria and diphtheroid organisms?

M.D., North Dakota.

ANSWER.—1. One experienced in the examination of diphtheria organisms can differentiate on smear, in the vast majority of instances, between a true diphtheria bacillus and a diphtheroid. However, it is not possible to distinguish by smear examination the difference between virulent and nonvirulent diphtheria bacilli. 2. No. 3. Yes. 4. If it is determined to one's satisfaction that the organism is a diphtheroid, a virulence test would not be necessary. 5. The tellurite technic would be of no value for determining the virulence of diphtheria organisms.

ACNE

To the Editor:—Kindly outline the latest treatment of acne simplex and acne vulgaris in an adolescent male aged 19. Is roentgen treatment preferable to cold quartz? Do emotional factors play a part?

M.D., New York.

ANSWER.—Treatment in these cases depends on the severity of the acne. If the lesions are superficial, small and not too disfiguring, satisfactory results can be obtained by a combination of topical therapy and some simple dietary restrictions. A sulfur preparation such as lotio alba should be applied every night to the point of producing slight exfoliation. The patient should be instructed to avoid the following in his diet: seafoods; foods that produce flushing of the skin, such as hot dishes, spices and alcohol; foods rich in fats, particularly chocolate, cheese, nuts, fat meats and gravy. The face should be cleansed thoroughly with soap and water two or three times a day, and the patient should not engage in an occupation which exposes him to oils or greases. If there is constipation or anemia, these should be brought under control. In recent years vitamin A, vitamin B, thyroid substance and estrogenic substance have been recommended, but their efficacy is still a matter for debate. Blackheads should be removed by the proper expressor and cystic lesions should be incised with a very small blade, as an iris knife. For persistent, deep-seated lesions roentgen therapy is still the treatment of choice and is preferable to use of the cold quartz mercury vapor lamp. The influence of emotional factors usually is not great; rather, acne is likely to affect the emotions.

LEUKEMIA

To the Editor:—Has leukemia, especially acute lymphatic leukemia, ever been produced experimentally? Is there a cerebral center which regulates formation of blood, especially white blood cells? Can this center be disturbed by trauma or regulated by drugs?

M.D., Pennsylvania.

ANSWER.—Leukemia of all types (lymphatic, myelogenous and monocytic) has been produced experimentally in mammals by numerous agents including radiation, hormones and various chemicals. It also occurs spontaneously in many animals. The picture resembles more the chronic leukemias in the human. In chickens there is a spontaneous disease, similar to human leukemia, caused by a virus.

The existence of a cerebral center for the regulation of blood formation has never been established, although there have been speculations as to the role of the pituitary and hypothalamus. The possible effects of drugs or trauma on such a hypothetic center would therefore be a matter of conjecture only.

Forkner quotes four authors who each described acute leukemia following injury to bones. However, the available evidence for a cause and effect relationship does not seem to be clearcut.

CESAREAN SECTION

To the Editor:—The general opinion is that it is "not safe to have more than two caesarian sections"—hence sterilization is performed routinely at the second section. Further, "once a section, always a section," regardless of normal pelvis, position. Is this correct?

M.D., Arizona.

ANSWER.—Theoretically each additional pregnancy after cesarean sections might involve increased risk of rupture of the uterine scar, and the operations might become more and more difficult because of adhesions; in practice, however, the likelihood of these accidents is minimal with laparotrachelotomy. Ordinarily there is no limit to the number of sections which a healthy woman may safely undergo. As many as eight sections have been done on some patients.

Sterilization is obviously indicated in a patient suffering from some condition such as grave cardiac or renal disease, which would make another pregnancy hazardous. It may also be considered as an elective procedure at the second or a later caesarean section in a healthy woman if she and her husband decide, after mature consideration, that their desire for another child is not great enough to warrant the ordeal of a laparotomy.

The dictum "once a cesarean always a cesarean" holds good when the first operation is done for contracted pelvis or some other abnormality which would equally complicate all subsequent deliveries. But if the first section is performed because of a condition incidental to that one pregnancy, for example, placenta previa or preeclamptic toxemia, it is frequently possible for later deliveries to be effected from below, especially if the patient has already borne a child *per vias naturales*. Labor in such a case should be watched with special care, and everything should be ready for laparotomy if there is any indication of thinning of the uterine scar.

"DICUMAROL"

To the Editor:—The administration of "dicumarol" for a relatively prolonged period of time is sometimes indicated. There are many disadvantages such as the necessity for the periodic determination of prothrombin levels, which is costly. This drug is primarily for the purpose of reducing the coagulability of the blood. Is it a more rational and practical procedure to regulate the dosage of the agent by determining the coagulability, rather than the prothrombin activity, of the blood?

M.D., Illinois.

ANSWER.—Determination of coagulation time cannot be substituted for that of prothrombin time in regulating the dosage of "dicumarol," because the coagulation time is little affected at the level of prothrombin (20 per cent of normal), which is desired for therapeutic effectiveness. It is only when the prothrombin is reduced to an exceedingly low concentration that a significant prolongation of the coagulation time occurs (Quick, A. J.: *J. Biol. Chem.* **161**:33 [Nov.] 1945).

Even if the coagulation time was suitable for testing quantitatively the action of "dicumarol," the obstacle of trustworthy technic still remains. The determination of the coagulation time by the capillary method, as commonly carried out, is meaningless and worthless. Only when the determination is performed by the Lee White technic under carefully controlled conditions are reliable results obtained; and this entails practically as much skill and effort as the prothrombin time method. The prothrombin test remains the only trustworthy means to control "dicumarol" therapy. Since it is becoming a routine hospital laboratory procedure, it should soon become available to most physicians.

FURUNCULOSIS

To the Editor:—For two years I have been treating a girl aged 4 years for repeated attacks of furunculosis. Sulfonamide drugs and penicillin (both internally and externally), a full course of autogenous vaccine and staphylococcus endotoxoid have been used without effect. Furuncles continue to develop every few months. Foci of infection are absent. Urinalysis is normal. Her health is otherwise good. Her parents are in good health. Please suggest other methods of treatment.

Jacob Greenblatt, M.D., Stamford, Conn.

ANSWER.—Occasionally, satisfactory results are obtained by the simple procedure of having the patient's entire body sponged twice a day with a solution of bichloride of mercury, 1:10,000. The underclothing should be changed daily and the outer clothing cleaned frequently. Generalized ultraviolet baths are often helpful, and the intake of carbohydrates should be restricted. One must be certain that the child is not receiving bromides or iodides, which occasionally will produce furunculous lesions in sensitized persons. A sugar tolerance test might reveal useful information.

If in spite of this regimen a new outbreak of furunculosis should occur, it might be well to administer penicillin again in large amounts and for a longer period, along with roentgen therapy to the lesions.

SYPHILIS

To the Editor:—A boy aged 16 had a severe attack of acute rheumatic fever at the age of 10 years. He was confined to bed for six months. Wassermann examination at that time revealed a 4 plus reaction. Examination since that time reveals no signs of syphilis other than positive blood tests. Serologic tests for syphilis on the blood and spinal fluid of the mother and on the blood of two other children in the family have been negative. The father of the patient died with Hodgkin's disease. The patient had recurrent acute rheumatic fever two years ago, but the attack was mild and there is now no evidence of rheumatic fever. Repeated Kolmer and Kahn tests on the blood of the patient have been strongly positive. Should he be told that he has a false positive test, or should antisyphilitic treatment be administered and a quantitative Kahn examination of his blood be made at regular intervals? M.D., Texas.

ANSWER.—It is stated that the examination does not reveal signs of syphilis. Was a lumbar puncture done? Moreover, it is not stated how many units of reagin were present in the patient's blood. In certain diseases with reversal of the albumin globulin ratio, e. g., granuloma inguinale, lymphogranuloma venereum and subacute disseminated lupus erythematosus, a false positive serologic test for syphilis occasionally occurs.

This patient should have a lumbar puncture, and if that is negative, much would depend on the degree of positivity in terms of Kahn units. One would hesitate to treat the patient for syphilis unless the test showed a high number of units. Occasionally a syphilis insontium does occur, and that must be considered as a possibility if the boy has a large number of Kahn units. Under those conditions, it might be well to give this boy, after a short course of intramuscular injections of bismuth subsalicylate, once a week for six or eight weeks, a course of crystalline penicillin G, 7,200,000 units, the injections being given intramuscularly every three hours over a period of two weeks.

REFRIGERANT GASES

To the Editor:—Please give me information regarding the toxic effects, if any, resulting from gases used in refrigeration, namely, methyl chloride and dichlorofluoromethane. The patient is a maintenance and installation mechanic for refrigeration units.

Cecil C. Shaw, M.D., Loxley, Ala.

ANSWER.—Dichlorodifluoromethane, known under the trade name of "freon," is a colorless, nontoxic refrigerant. R. R. Sayers, W. P. Yant, J. Chornyak and H. W. Shoaf (Industry Report 3013, United States Department of Commerce, Bureau of Mines, May 1930) report on the toxicity of dichlorodifluoromethane as follows "In so far as the results of animal experimentation serve as a measure of hazards to persons, the investigation has shown that the possibilities of public health and accident hazards resulting from exposure to dichlorodifluoromethane when used as a refrigerant are remote."

Methyl chloride as used in the refrigeration industry is a colorless liquid with an ethereal odor and a sweetish taste. It is inflammable and explosive as well as toxic. Acute poisoning is attended by headache, dizziness, mental confusion, nausea and vomiting, lowering of blood pressure and, in serious cases, cyanosis, cramps and coma. Chronic cases are characterized by increasing fatigue, lassitude, muscular weakness, restlessness and occasionally, insomnia.

Most cases of individual poisoning are due to repeated exposure to small doses which gradually cause injury to the central nervous system. Exposure to 200,000 parts per million for one hour is dangerous to life; exposure to 500 parts per million is a safe working condition for a few hours, according to California law.

CATARACT

To the Editor:—A patient has a mature cataract in the left eye and incipient in the right eye. Recently he consulted an oculist and was given the following treatment. Synthetic thyroxin (2 mg. to each cc. distilled water) to be dropped in eye three times daily. He was told that in many instances this would retard if not improve his condition. Please give information regarding this treatment.

Ralph C. Wise, M.D., Mansfield, Ohio.

ANSWER.—Thyroxin was first used in 1934 by Jameson on the theory that thyroxin exerted a local stimulating effect and acted as an alternative. His dosage was 1 mg. to the cubic centimeter used locally on the eyeball. He reported beneficial results both in limiting the growth of cataract formation and in the absorption of existing opacities. In 1941 Gillette repeated some of Jameson's work and did a series of his own; he came to the conclusion that thyroxin locally (1) does not check the development of senile lens opacities (2) does not cause the absorption of existing opacities and (3) has no demonstrable metabolic effect. Vail seems to be of the same opinion as Gillette. At the present time there seems to be little clinical evidence that thyroxin is of any use in preventing further growth of cataract or in absorbing existing lens opacities.

STERILITY

To the Editor:—I have a male patient, aged 40, with relative sterility. His history is essentially noncontributory, but he recalls that his left testicle was traumatized at 13 years of age. Physical conditions are normal except that the left testicle is about half the size of the right. Both testes are of normal consistency. The prostate is slightly enlarged and somewhat boggy. Results of urinalyses and the Wassermann test are negative. Hemoglobin and the white blood cell count are within normal limits. The basal metabolic rate is minus 12 per cent. The volume of ejaculated semen is about 2.5 cc., with a sperm count of 10 million. Motility of sperm is somewhat sluggish. I did not determine the percentage of abnormal forms, but on ordinary microscopic examination some abnormal spermatozoa are seen. I am treating this patient with vitamin E and thyroid. Is other therapy recommended? What are this man's chances of attaining a normal level of fertility? M.D., Ohio.

ANSWER.—Before any elaborate program of treatment is undertaken, the cell structure of the spermatozoa should be evaluated. If there proves to be a high incidence of abnormal forms, then a biopsy of this patient's right testicle is indicated. This will help to judge whether the germinal epithelium is capable of responding to stimulation. The first step in treatment is careful attention to hygiene and general health, with special reference to outdoor exercise, rest and relaxation, adequate protein in the diet and the possibility of chronic focal infection. The prostatovesicular secretions should be examined.

Endocrine therapy deserves a trial, though results are often discouraging. Pregnant mare's serum, other chorionic gonadotropins and pituitary gonadotropins might be used seriatim, since there is no way of predicting which offers the best chances of benefit. While large doses of sex hormones inhibit the anterior pituitary, very small doses of testosterone sometimes readjust the pituitary-gonad balance in such a way as to increase the gonadotropic output.

A postcoital examination (Hühner test) done at the wife's midcycle will show how well the spermatozoa are able to invade the endocervical mucus. If a defect in this regard is observed, attention should be directed to possible abnormalities of the mucus, such as scantiness or infection, and appropriate treatment should be instituted.

Relative infertility in one partner may be overcome by high fertility in the other. Hence, the wife should be critically studied with the idea of finding and eliminating all factors of infertility.

Efforts to improve the values of deficient semen are usually attended by rather meager success. Nevertheless, definite improvement may be obtained in a few cases.

CORRECTION: PERTUSSIS VACCINE

To the Editor:—In the Dec. 13, 1947 issue of *The Journal*, page 1040, under "Vaccination against Pertussis," there is an error in the second paragraph on the dosage of Sauer pertussis vaccine alum precipitated.

The alum precipitated pertussis vaccine prepared according to the Sauer specifications contains 30 billion Hemophilus pertussis bacilli per cubic centimeter, and the recommended dose is 0.5 cc. per injection at one month intervals. Four injections are recommended if immunization is attempted before the sixth month of life, or three doses if injections are begun after 6 months of age. It is recommended that injections be made in the buttocks, alternating from left to right, care being taken not to make a second injection in a site previously used.

The dosage described in the article referred to is for the plain H. pertussis vaccine, which should be used only after the child is 6 months of age or older. When alum precipitated pertussis vaccine is administered in dosage greater than 0.5 cc. an area of softening may be caused by the alum, which is known as "alum cyst." Occurrence of such cysts is infrequent but can be avoided by using small doses of the vaccine.

Louis W. Sauer, Evanston, Ill.

PENICILLIN—STREPTOMYCIN

To the Editor:—On page 745 of the Nov. 15, 1947, issue of *The Journal* is an answer to a query which might well be further elaborated. It is true that, in general, penicillin and streptomycin are compatible, at least as far as the antibiotics themselves are concerned. However, if streptomycin sulfate should be mixed with calcium penicillin, of which a significant amount is still sold, a precipitate of calcium sulfate would be inevitable. I thought it might be well to elaborate on this point, because otherwise some one might get an unwelcome surprise.

Robert D. Coghill, Director of Research,
Abbott Laboratories,
North Chicago, Ill.

POSSIBLE INCOMPATIBILITY OF STREPTOMYCIN AND PENICILLIN

To the Editor:—In the Nov. 15, 1947, issue of *The Journal*, page 745, I note that in answer to an inquiry concerning the possibility of giving streptomycin and penicillin in the same syringe the reply states that there is no incompatibility. I think the situation has been overlooked in which aqueous solutions of calcium penicillin and streptomycin sulfate might be mixed, with the consequent formation of calcium sulfate as an insoluble precipitate.

George Rieveschl Jr., Detroit 32.

V 136
1948